

among females. For drug-related adverse events, the numbers between the genders are closer together, 27% for females over 23% for males. This slightly higher incidence in females was accounted for by the cases of vaginitis and other events such as nausea and abdominal pain. Dry mouth, taste perversion, vomiting, and flatulence was slightly more common among males. The analysis of laboratory abnormalities by gender revealed a few differences. The overall incidence of serum transaminases elevations was higher in men than women, and was most notable for AST (12% vs 6%), anemia \*8% vs 3%), and elevations in bicarbonate (15% vs 6%).

*MO COMMENT: The applicant's attention to gender inclusion and analysis was appropriate to the indication being studied.*

### **B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

Patients ranging from 18 years to 86 years of age were included in these protocols. Efficacy results were not separately analyzed by age, but safety results were. The incidence of adverse clinical events of all causes was higher in the elderly population: 62% among those aged 65 to 74 and 56% among those >75 years old, compared to 38% among those less than 65. Dyspnea, cough, and sputum production, all likely to be related to the underlying infection, were the most frequent adverse events in the 65-74 age group. Dyspnea, chest pain, dizziness and rhinitis were the most frequent events for those  $\geq 75$  years of age. Likewise for drug-related adverse events, the overall incidence was highest among patients between 65 and 74 years of age (31%); diarrhea accounts for much of the difference. Dizziness was most frequently seen in patients  $\geq 75$  year old, although the numbers are very small. Although numbers are small, there was a trend towards more laboratory abnormalities in patients that were  $\geq 65$  years of age. Among these were anemia, elevations in BUN and creatinine, decreases in chloride, and increases in bicarbonate.

The vast majority of randomized patients were White (84%) with Blacks being the next largest race group at 10%. Hispanic, Asian, Alaskan Native, and Filipino accounted for the remaining 6% (Other) of the study population. The applicant's safety analysis showed that the overall incidence of gatifloxacin-related adverse clinical events was slightly higher in White and Other patients at 26% each and lower among African-Americans at 21%. African-Americans reported less diarrhea than other groups. In the applicant's analysis of laboratory data by race, a number of abnormalities were more frequently noted in the African-American population; among these were changes in hematologic parameters, particularly neutropenia, and elevation in AST.

*MO COMMENT: The applicant's attention to age, race, and ethnic groups was appropriate for the indication being studied.*

### **C. Evaluation of Pediatric Program**

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### **D. Comment on Other Special Populations**

Previous studies with gatifloxacin have resulted in labeling for special populations. The current label includes a special populations section as well as sections for pregnancy and nursing mothers. This drug is

Pregnancy category C. In the studies leading to this current supplemental application, patients with renal or hepatic insufficiency as well as patients who were pregnant or lactating were excluded. Patients with significant immune dysfunction (i.e. AIDS) were also excluded from these studies.

*MO COMMENT: The exclusion of patients with immune, hepatic, and renal insufficiency makes it difficult to predict safety and efficacy in these population groups.*

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## X. Conclusions and Recommendations

### A. Conclusions

Gatifloxacin (Tequin®) is currently approved for the treatment of AECB. The approved treatment regimen is 400 mg (oral or intravenous) given once daily for 7-10 days. In these supplemental New Drug Applications (21-061 and 21-062), the applicant has submitted two controlled clinical trials, studies 064 and 065, to support reducing the duration of treatment for AECB to 5 days. Study AI420-064 included both 5- and 7-day gatifloxacin treatment arms; the comparator was clarithromycin (500 mg PO BID for ten days). Study AI420-065 compared a 5-day course of gatifloxacin with a standard 5-day course of azithromycin (500 mg PO on Day 1, followed by 250 mg PO on Days 2-5).

Results from the two pivotal studies are summarized below.

NDA# 21-061/ S-007 and 21-062/ S-008 5-day gatifloxacin for AECB Medical Integrated Review

<b>Study 064: Double-blind, randomized 3 arm trial, 1:1:1 in 35 US sites. Total enrolled = 532 patients (197 patients from sites 23 and 24 excluded in analysis due to DSI investigation)</b>			
<b>Mean age 53 years; 86% White; 83% Type I exacerbation; 1<sup>o</sup> population: Clinically Evaluable Pts</b>			
	<b>5 day gatifloxacin (400 mg QD)</b>	<b>7 day gatifloxacin (400 mg QD)</b>	<b>10 day clarithromycin (500 mg BID)</b>
<b>All Enrolled (+23/24)</b>	<b>N=175</b>	<b>N=176</b>	<b>N=181</b>
<b>Enrolled (-23/24)</b>	<b>N=110</b>	<b>N=114</b>	<b>N=111</b>
<b>Treated</b>	<b>N=109</b>	<b>N=113</b>	<b>N=108</b>
<b>Clinically Eval</b>	<b>97/109 (89%)</b>	<b>102/113 (90%)</b>	<b>101/108 (94%)</b>
<b>Microbiol Eval</b>	<b>43/109 (39%)</b>	<b>43/113 (38%)</b>	<b>41/108 (38%)</b>
<b>Outcome (-23/24)</b>			
<b>Clinically Eval*</b>	<b>86/97 (89%)</b>	<b>86/102 (84%)</b>	<b>86/101 (85%)</b>
<b>Microbiol Eval</b>	<b>N=51 total pathogens</b>	<b>N=49 total pathogens</b>	<b>N=42 total pathogens</b>
<b>Eradication (-23/24)</b>	<b>Total = 49/51 (96%)</b>	<b>Total = 44/49 (90%)</b>	<b>Total = 40/42 (95%)</b>
<i>H. influenzae</i>	12/12	12/13	8/8
<i>S. pneumoniae</i>	12/13	5/5	6/6
<i>M. catarrhalis</i>	11/11	8/10	11/11
<i>H. parainfluenzae</i>	5/5	5/6	2/4
<i>S. aureus</i>	9/10	14/15	13/13

\*95% CI: 5 day gatifloxacin vs 10 day clarithromycin (-5.3%, 12.3%)  
 5 day gatifloxacin vs 7 day gatifloxacin (-4.4%, 13.6%)  
 7 day gatifloxacin vs 10 day clarithromycin (-12.7%, 6.9%)

<b>Study 065: Double-blind, randomized 3 arm trial, 1:1 in 20 US sites. Total enrolled = 296</b>		
<b>Mean age 52 years; 80% White; All Type I exacerbation; 1<sup>o</sup> population: Clinically Evaluable Pts</b>		
	<b>5 day gatifloxacin (400 mg QD)</b>	<b>5 day azithromycin (500 mg day 1; 250 mg days 2-5 QD)</b>
<b>All Enrolled</b>	<b>N=147</b>	<b>N=149</b>
<b>Treated</b>	<b>N=147</b>	<b>N=147</b>
<b>Clinically Eval</b>	<b>127/147 (86%)</b>	<b>125/147 (85%)</b>
<b>Microbiol Eval</b>	<b>73/147 (50%)</b>	<b>74/147 (50%)</b>
<b>Outcome (-23/24)</b>		
<b>Clinically Eval*</b>	<b>104/127 (82%)</b>	<b>92/125 (74%)</b>
<b>Microbiol Eval</b>	<b>N=88 total pathogens</b>	<b>N=87 total pathogens</b>
<b>Eradication (-23/24)</b>	<b>Total = 75/88 (85%)</b>	<b>Total = 69/83 (83%)</b>
<i>H. influenzae</i>	11/12	15/18
<i>S. pneumoniae</i>	6/7	8/9
<i>M. catarrhalis</i>	24/26	14/16
<i>H. parainfluenzae</i>	18/22	13/18
<i>S. aureus</i>	16/19	19/22

\*95% CI: 5 day gatifloxacin vs 5 day clarithromycin (-3.4%, 17%)

Study 064 and 065 Combined Eradication rates (Microbiologically Evaluable Patients)		
	5 day gatifloxacin	Comparator arms combined: clarithromycin and azithromycin
Eradication Rates	Total = 124/137 (91%)	Total = 109/125 (87%)
<i>H. influenzae</i>	23/24 (96%)	23/26 (88%)
<i>S. pneumoniae</i>	18/20 (90%)	14/15 (93%)
<i>M. catarrhalis</i>	35/37 (96%)	25/27 (93%)
<i>H. parainfluenzae</i>	23/27 (85%)	15/22 (68%)
<i>S. aureus</i>	25/29 (86%)	31/34 (91%)

Eight hundred and twenty-eight patients totaled the safety database for these supplements and included the patients enrolled into sites 23 and 24 of the 064 study. Forty-two percent (n=208/496) of the gatifloxacin-treated patients and 44% (n=143/325) of comparator-treated patients reported at least one adverse event. Drug-related adverse events were seen in 25% of (n=124/496) gatifloxacin-treated patients and 22% (n=70/325) of comparator-treated patients. Pooled drug-related adverse rate across the two studies for 5-day gatifloxacin treatment arm was 23% (n=75/321) whereas for 7-day gatifloxacin arm, the rate was 28% (n=49/175). The most common events among gatifloxacin-treated patients were diarrhea, nausea, and dry mouth, while diarrhea, taste perversion, and nausea were most frequently cited among comparator-treated patients. There was no evidence that gender or race influenced the incidence of adverse events; patients  $\geq$  65 years of age had a slightly higher incidence of adverse events. Laboratory abnormalities were uncommon, and Grade 3 or 4 severity abnormalities very rare. Hyperglycemia was more noted in gatifloxacin-treated group than in the comparator group. For patients with normal pre-treatment laboratory values in the 065 study, Grade I hyperglycemia was noted in 4 (25%) of 16 tested patients in the gatifloxacin arm in comparison to none in the azithromycin arm. In total, eight gatifloxacin-treated patients (2%) and eight comparator-treated patients (2%) discontinued study therapy because of adverse events, usually either respiratory symptoms related to the underlying infection or gastrointestinal intolerance.

The use of Tequin® in special populations is discussed in detail under section XI of the integrated review. Briefly, the applicant's attention to gender, age, race, and ethnic group inclusion and analysis was appropriate to the indication being studied.

Tequin is currently labeled as Pregnancy category C. Pregnant or nursing women was excluded from these AECB studies, which was appropriate. Patients with immune, hepatic, and renal insufficiency were excluded in these AECB studies as well. Exclusion of these patients makes it difficult to predict safety and efficacy for AECB treatment in these population groups.

## B. Recommendations

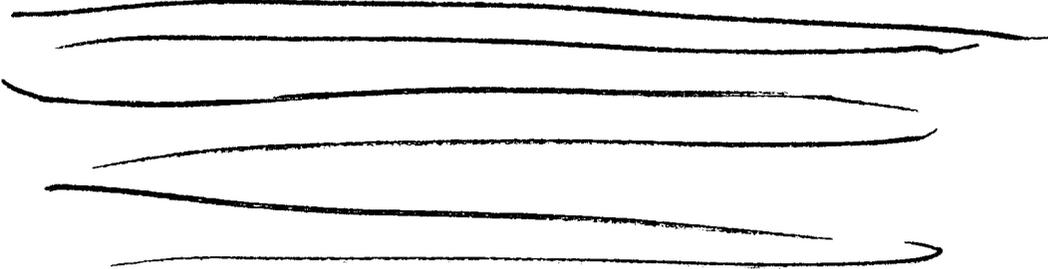
The data presented in this application support the use of gatifloxacin for 5-day treatment of acute exacerbations of chronic bronchitis. Equivalence to two approved treatments was demonstrated and the overall efficacy results were comparable, both in terms of clinical and bacteriologic efficacy. Safety profile of gatifloxacin in these trials was favorable. Thus, the evidence of effectiveness and the appearance of adequate safety support the regulatory action of approval.

Several labeling issues need to be addressed.

### With this action

- 1) The applicant proposes to withdraw the 7-10 day duration stated in the current package insert and replace with 5-days duration for the AECB indication. *This is agreeable.*

- 2) Several re-arrangement changes are proposed under the safety section with the re-tabulated data of "over 5000 patients" treated in clinical trials from "over 4000 patients" as stated in the current insert. *These wording and percentage changes are acceptable.*



**XI. Appendix**

- A. Study 064** (see attached)
- B. Study 065** (see attached)
- C. OPDRA Consult**

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**APPENDIX #1:APPLICANT'S STUDY AI420-064**

**A Randomized, Double-Blind, Multi-center, Comparative Study  
of Gatifloxacin Versus Clarithromycin in the Treatment of Acute  
Exacerbation of Chronic Bronchitis (AECB)**

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Gatifloxacin (Tequin®) is an 8-methoxy fluoroquinolone that is currently approved for a 7-10 day course treatment of acute exacerbation of chronic bronchitis. In this current supplemental NDA, the applicant (Bristol-Myers Squibb Company) is seeking approval for 5-day duration of therapy for the treatment of acute exacerbation of chronic bronchitis. The dose proposed is 400 mg once a day (both intravenous or oral), and the age group is 18 years and above inclusive. This is one of two pivotal trials submitted to support the approval of these efficacy supplements.

### **Rationale/Objective**

The rationale given for seeking a 5 day regimen for the AECB indication was that shorter-course therapy would increase compliance and convenience, result in fewer side effects, lower costs, and decrease bacterial resistance. The applicant also pointed out that Avelox (Moxifloxacin – Bayer) was granted approval for 5-day treatment of AECB.

The primary objective of this study (aI420-064) was to demonstrate equivalent clinical efficacy of 5-day gatifloxacin treatment in AECB relative to a standard 10-day course of clarithromycin. As per the applicant, Clarithromycin was chosen as the comparator for this trial because it has been approved by the FDA for the AECB indication and efficacy has been demonstrated in several trials.

The secondary objectives were to demonstrate clinical efficacy of a 7-day course of gatifloxacin versus 10-day course of clarithromycin, demonstrate clinical efficacy of a 5-day course of gatifloxacin compared to a 7-day course of gatifloxacin, and to document bacteriologic efficacy of all three therapeutic options. Also included in the secondary objectives were to evaluate the safety of all three therapeutic options.

### **Design**

This was a randomized, comparative, double-blind, multicenter study that would assess the efficacy of gatifloxacin, 400 mg PO daily for 5 days in comparison to a standard 10 day regimen of clarithromycin (500 mg PO BID), or gatifloxacin 400 mg PO once a day for 7 days (7-day gatifloxacin) for the treatment of adults with AECB. Patients were randomized to receive one of three dosing regimens and stratified based on systemic steroid use at the time of randomization. Forty-eight investigators in the US were recruited and 35 sites enrolled patients. The target enrollment was 564 subjects (188 per arm) patients with a 1:1:1 randomization to one of the three treatment groups. The sample size was determined using a cure rate of 80% for clarithromycin arm. Assuming equivalence in response rates between the clarithromycin group and the 5-day gatifloxacin arm and 90% power to rule out a maximum difference of 15%, 150 evaluable patients per arm were needed. A reassessment of sample size occurred after 120 patients were enrolled. Based on the observed evaluability rate of 90%, the total accrual was revised to 500 patients. ( from 564 patients when evaluability rate was estimated at 80%).

***MO COMMENT: This trial attempts to establish equivalence of 5 day gatifloxacin treatment to two approved regimens for the indication of AECB: 10 day treatment with clarithromycin, and a 7 day treatment with gatifloxacin. The study design uses an active control drug and a random assignment of patient to the investigational drug or the active control drug groups in a double-blind fashion. This is the preferred design according to the IDSA/FDA "Guidelines For The Evaluation of Anti-Infective Drug Products".***

## **Protocol**

### **Study Population**

#### **Inclusion and Exclusion**

For inclusion, patients with a history of chronic bronchitis (i.e. productive cough on most days for at least three consecutive months in two consecutive years) and a diagnosis of AECB had to meet all of the following criteria:

- 1) Eighteen years of age or older
- 2) Clinical diagnosis of acute exacerbation of chronic bronchitis, defined as:
  - The presence of purulent sputum confirmed by Gram stain examination [ $>25$  polymorphonuclear leukocytes (PMN) per low power field (LPF)]
  - The presence of at least two of the following signs and symptoms:
    - increase cough and/or dyspnea
    - increased sputum volume
    - increased sputum purulence
- 3) For women of childbearing potential:
  - A negative urine pregnancy test within two days prior to enrollment
  - A commitment to use an effective method of contraception from the start of study treatment to use an effective method of contraception from the start of study treatment until the end of their participation in the study
- 4) Written informed consent (from patient or their guardians) before any study procedure were performed

Patients were excluded if they met any of the following criteria within 2 days prior to randomization:

- 1) Pregnant or lactating
- 2) History of significant hypersensitivity reaction to any quinolone or macrolide/azalide antibiotic
- 3) Received a systemic antibiotic therapy within seven days prior to randomization, or were likely to require other systemic antibiotic(s) concomitantly
- 4) Diagnosis of pneumonia confirmed by the presence of pulmonary infiltrates on a chest x-ray
- 5) Previously diagnosed disease(s) of immune function (e.g. AIDS or history of clinical manifestations of HIV infection, neutrophil count  $<1000/\text{mm}^3$ )
- 6) Previously diagnosed condition that would tend to mimic or complicate the course and evaluation of the infectious process
- 7) Known renal insufficiency (i.e. serum creatinine 1.5 times the upper limit of normal)
- 8) Known or suspected clinically significant hepatic disease (i.e. aspartate amino transferase [AST] and/or alanine amino transferase [ALT] and/or total bilirubin 3 times the upper limit of normal)
- 9) Malabsorption syndromes or other gastrointestinal disturbances that would affect drug absorption
- 10) Previous treatment in any gatifloxacin AECB clinical trials

***MO COMMENT: Inclusion and exclusion criteria were clearly identified prior to initiation of the study. Patients with exacerbation Type 1 and Type 2 (see below) were included in this study. This is different from trial 2 where only Type 1 was included. Also different from trial 2 was randomization by systemic corticosteroid use only. The exclusion of patients with AIDS, renal insufficiency, and hepatic disease makes it difficult to predict safety and efficacy in these population groups.***

Exacerbation type at entry was determined according to the following criteria established by Anthonisen, et al.

- Type I: increase dyspnea, increase sputum volume and increased sputum purulence
- Type II: any two of the three symptoms of Type I
- Type III: any one of the three symptoms of Type I

**MO COMMENT:** *Anthonisen et al. used the above criteria in an AECB study that was published in the Annals of Medicine in 1987(106:196-204). His inclusion criteria required that all patients enrolling into the trial have a baseline pulmonary obstructive disease as defined by FEV<sub>1</sub> < 70% and be no younger than 35 years of age. This is very different than what was done in this trial. The only requirement for entry into this protocol was to have "productive cough on most days for at least three consecutive months in two consecutive years". There were no objective measurements to ensure that patients being enrolled into the protocol had true baseline pulmonary disease.*

Patients received one of three treatments: gatifloxacin 400 mg orally once a day for 5 days, gatifloxacin 400 mg orally once a day for 7 days, or clarithromycin 500 mg orally BID for 10 days. These treatments were coupled with appropriate placebo in "double dummy" fashion. There were no provisions for dose modification. Patients were asked to fill in a medication diary to encourage compliance.

**MO COMMENT:** *The primary comparator CLARITHROMYCIN is currently labeled in the treatment of AECB at the following doses for the different pathogens: H. influenzae -500 mg BID for 7-14 days, H. parainfluenzae -500 mg BID for 7 days, M. catarrhalis -250 mg BID for 7-14 days, and S. pneumoniae -250 mg BID for 7-14 days. Thus, the dose used in this study namely 500 mg BID for 10 days was appropriate.*

Patients were excluded if they had received antibiotic therapy within 7 days before enrollment. Other antimicrobial agents, such as antivirals and antifungals, were permitted. Adjunctive measures, such as oral or topical decongestants, antihistamines, and intranasal steroids, were permitted during and post-treatment as needed by the patient. In addition, concomitant or post-treatment non-drug therapies, such as postural drainage or oxygen were allowed. Investigators were permitted to discontinue study drug and remove patients from the study for the following reasons:

- An adverse event
- Persistence or worsening of signs and symptoms of the acute infection after three days of study drug therapy
- An intercurrent illness
- Patient's decision not to participate any further
- Investigator's decision that discontinuation was in the patient's best interest
- A female patient with a positive pregnancy test during study drug therapy (immediate discontinuation)
- Investigator's decision that discontinuation was in the patient's best interest
- Decision of the applicant to terminate the study (at some or all sites)

Patients with one or more study drug-resistant pre-treatment pathogens were removed from the study if the investigator felt it was in their best interest. Patients whose condition had not improved or had worsened after 3 days of study drug therapy (early treatment failures) were removed from the study. These patients had the same clinical and laboratory procedures performed as those specified for the past-treatment visit scheduled for Day +7 to Day +14 before starting alternative antibiotic therapy.

#### Patient Assessments

Patient assessments were scheduled to occur as follows (Table 2):

- Pre-treatment (within 48 hours before dosing) office/clinic visit
- During treatment (Day 3 to Day 5) office/clinic visit
- End of treatment (Day +1 to Day +3) telephone contact (office/clinic visit for further evaluation if not clinically improved)
- Post-treatment (Day +7 to Day +14) office/clinic visit (Test-of-Cure)
- Extended Follow-up (Day +21 to Day +28) telephone contact

**Table 1: Schedule of Patient Assessments**

Procedure	Pre-treatment (Within 2 days prior to dosing)	During Treatment (Days 3 to 5)	End of Treatment <sup>a</sup> (Days +1 to +3)	Post-Treatment (Days + 7 to +14)	Extended Follow-up <sup>a</sup> (Days + 21 to +28)
Screening <sup>c</sup>	X	--	--	--	--
Chest X-Ray	X	X	--	X	--
Medical History	X	--	--	--	--
Physical Exam	X	--	--	X	--
Vital Signs	X	X	--	X	--
Clinical Evaluation	X	X	X	X	X
Laboratory Tests	X	X	--	X	--
Sputum Smear and Evaluation	X	X <sup>b</sup>	--	X <sup>b</sup>	X <sup>b</sup>
Sputum Culture	X	X <sup>b,c</sup>	--	X <sup>b,c</sup>	X <sup>b,c</sup>
Assess adverse events	--	X	X	X	X
Assess Medication Use	--	X	X	X	--
Pregnancy Test	X	X	--	X	--

<sup>a</sup> Telephone contact. If patient not clinically improved, office visit to be scheduled for further evaluation

<sup>b</sup> If sputum production persists.

<sup>c</sup> If a purulent sputum is obtained

A central laboratory performed all laboratory procedures, including appropriate cultures. Investigators performed initial Gram stain procedures on site to expedite determination of sputum purulence and, therefore, patient eligibility. The Central laboratory performed an independent sputum Gram stain and would overread the smear provided by the site. Results from the central laboratory's Gram stain and their overread were made available to the Investigator within 24-48 hours of a patient's enrollment. A qualifying result (i.e. >25 PMN/LPF) from either of the two sputum Gram stains was sufficient for the patient's continued participation in the study.

All sputum specimens were plated semi-quantitatively for aerobic growth, and all potential pathogens isolated were tested for susceptibility to gatifloxacin and clarithromycin. Hematology, serum chemistry, and urinalysis tests included: White blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, and microscopic urinalysis. A urine pregnancy test was performed on all women of childbearing potential. Positive urine pregnancy tests were confirmed with a serum-based pregnancy test. All pre-treatment procedures were performed within two days prior to the start of study medication.

Patients were seen at least once during treatment (between Day 3 and Day 5, inclusive). Clinical evaluation as well as laboratory tests were performed. A chest x-ray was taken if clinically indicated. In the three day period immediately following the end of therapy (i.e., Day +1 to Day +3, inclusive), patients were contacted by telephone and queried about the clinical symptoms of infection, the occurrence of adverse events, and compliance with the dosing regimen. If a patient's signs and symptoms had not returned to baseline, or if clear clinical improvement had not occurred, the patient was scheduled for an immediate office visit.

Between seven and fourteen days post-treatment (i.e., Day +7 to Day +14, inclusive), patients were evaluated in the office/clinic for clinical and bacteriologic response to study drug therapy and the occurrence of adverse clinical events. If a patient is still producing sputum, a specimen was obtained for assessment of purulence, quantitative culture and susceptibility testing. If a laboratory test result became abnormal or worsened from an abnormal pre-treatment level, the test was repeated at appropriate intervals until the value either returned to the pre-treatment level or stabilized.

Patients who had a clinical response of cured at the Day +7 to Day +14 post-treatment visit were contacted by telephone approximately two weeks later (i.e., Day +21 to Day +28, inclusive) to assess relapse of the acute infection. Patients were queried about the presence and severity of clinical signs and symptoms of infection, the ingestion of any antibiotics since the last office/clinic visit, and the occurrence of adverse clinical events. If increased cough, dyspnea, and/or sputum purulence or production recurred after initial improvement, a sputum sample was assessed for purulence and if purulent, was submitted for bacteriologic culture and susceptibility testing.

*MO COMMENT: Patient monitoring was adequate in terms of frequency of visits and phone follow-ups. Laboratory tests were also adequate for proper detection of toxicity. However, study drug levels were not measured to verify compliance. Reliance on a central laboratory minimizes intersite variability and ensures consistency of test results.*

### Endpoints

Clinical and bacteriologic responses were determined from data at the TOC visit scheduled between Day +7 and Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit from Day +5 and Day +18, inclusive, was acceptable. Investigators assigned a clinical response to each patient and a bacteriologic response to each pre-treatment pathogen. If a patient did not have a post-treatment visit, a response was derived from any available data during or post-treatment. Each patient was assigned a clinical response of Cured, Failure, or Unable to Determine with every possible attempt at either a Cure or Failure assignment. For discrepancies between the Investigators and the BMS Medical Monitor where a consensus cannot be reached, the efficacy analyses were based on the responses assigned by the Medical Monitor.

### **Clinical Response**

#### **CURED at the Test-of-Cure Visit**

- All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, sputum purulence) have improved or returned to the patient's baseline level with the original therapy alone and without need for further antimicrobials; and
- No new signs or symptoms of acute infection were present.
- and if elevated at study entry, fever was resolved (i.e., temperature  $\leq 38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ )
- (Note: Baseline is defined as the patient's assessment of their typical/usual condition when free of acute infection).

#### **FAILURE:**

- New clinical signs and symptoms of acute infection appeared, or
- If present at study entry, the patient still has fever (i.e., temperature  $> 38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ ), or
- Clinical/radiological evidence of pneumonia; or
- Another antibiotic was required for treatment of this acute episode despite the resolution or improvement of signs and symptoms; or

- One or more signs and symptoms of acute infection have failed to improve after at least three consecutive days of study therapy

UNABLE TO DETERMINE:

- Per Analysis Plan: No follow-up beyond the pre-treatment visit.
- Per Protocol: No TOC visit evaluation or Receipt of another systemic antibiotic with documented activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to TOC visit

*MO COMMENT: It is important to note that to be CURED, the study subject had to have all signs and symptoms related to the acute infection "improved" or "returned to baseline". However, there were no objective measures of "improvement" or "returned to baseline" such as pulmonary function tests, symptom scores, etc. There was no grading of the symptoms. The signs/symptoms assessments were entirely subjective, i.e. patient reporting "my cough is better" and/or investigator reporting "sputum is less purulent". Thus, it was particularly important that trials for an indication such as AECB be conducted in a double-blinded control fashion to limit the bias of subjective clinical assessment.*

**Bacteriologic Response**

ERADICATED:

- The original pathogen was absent in the culture of a good quality (i.e., > 25 PMN/LPF) sputum specimen obtained at the TOC visit.

PRESUMED ERADICATED:

- The subject was not producing sputum (i.e., there was no source to culture); or
- No sputum was obtained, and the clinical response was CURED.

PERSISTED:

- The original pathogen was present in the culture of a good quality (i.e., > 25 PMN/LPF) sputum specimen obtained at the TOC visit.

PRESUMED PERSISTED:

- The subject was not producing sputum (i.e., there was no source to culture); or
- No sputum was obtained, and the clinical response was FAILURE.

UNABLE TO DETERMINE:

- The clinical response of the patient in question was designated Unable to Determine.

A by-patient bacteriologic response was computed for each patient with at least one pathogen isolated pre-treatment. The by-patient response incorporates the bacteriologic responses for all pre-treatment sputum pathogens isolated for a patient. For example, a patient with two pre-treatment pathogens, one eradicated and one persisted, was assigned the by-patient bacteriologic response of ERAD/PERS. No distinction was made between documented and presumed responses. **Persistent Pathogens** were tested for susceptibility to both study drugs as well as to other appropriate antibiotics. **Relapse** from the clinical response of Cured at the TOC visit was evaluated at the extended follow-up assessment (Day +21 to Day +28). A patient was considered to have relapsed if they were given an alternative antibiotic therapy because of signs and symptoms of an acute bronchial infections. Pathogens isolated from relapsed patients were speciated and tested for susceptibility to gatifloxacin, azithromycin and other antibiotics as appropriate. A new infection was defined as the occurrence, at any time during or after study therapy of one of the following: isolation of any pathogen from a new site of infection, with associated clinical signs and symptoms or the presence of clinical signs and

symptoms indicative of a new infection for which a culture would not usually be obtained (e.g., skin infection). Pathogens isolated from patients with new infections were speciated and tested for susceptibility to gatifloxacin, clarithromycin and other antibiotics as appropriate.

#### **Adverse Clinical Events**

Investigators reported all adverse events to the Applicant, along with their judgement of the causality. For the purpose of analysis, events that were certainly, probably, or possibly drug-related were grouped and categorized as "drug-related". Investigators also assessed the severity (mild, moderate, severe, or very severe) of each adverse clinical event.

#### **Abnormal Laboratory Results**

Any worsening in laboratory parameters during or post-treatment was categorized according to a severity grading scale derived from the National Cancer Institute's Common Toxicity Criteria (CTC) and the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) classification of laboratory abnormalities. Four grades of abnormality were defined (Grades 1-4), and the range of laboratory values associated with each grade was established for each test. Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the abnormal values returned to pre-treatment levels or were deemed by the investigator to be unrelated to the study medication.

*MO COMMENT: Clinical, microbiologic, and laboratory endpoints were adequately defined prior to study initiation.*

#### **Statistical Considerations**

##### **Data Set Descriptions (Four Study Populations of Interest)**

**ALL TREATED PATIENTS:** All patients who received at least one dose of study medication.

**ELIGIBLE PATIENTS:** All Treated Patients with a diagnosis of AECB at entry, defined as:

- A positive answer to the question "Has the patient coughed up sputum on most days for at least three consecutive months for at least two consecutive years?"
- Two or more of the signs/symptoms of AECB at study entry: increased dyspnea and cough, increased sputum production, and increased sputum purulence.
- Having a pretreatment radiograph that did not show pneumonia
- Evidence of purulence from an adequate pre-treatment sputum sample (>25 PMN/LPF) obtained within 2 days prior to start of treatment

**CLINICALLY EVALUABLE PATIENTS:** All Eligible Patients who

- Received at least 4 days of study medication (at least 3 for failures)
- Had a post-treatment clinical assessment within the Day +5 to Day +18 window for the TOC visit (except for failures)
- Did not receive a systemic antibacterial agent between the time of the pre-treatment visit and the post-treatment assessment

**MICROBIOLOGICALLY EVALUABLE PATIENTS:** All Clinically Evaluable Patients who had at least one pathogen isolated pre-treatment non-resistant (susceptible and intermediate) pre-treatment to either study drug.

*MO COMMENT: The 4 datasets correspond to the definitions for the indication of AECB in the initial gatifloxacin NDA application that was approved for 7-10 days duration.*

*FDA clinical efficacy analysis will utilize the following evaluability criteria which is in keeping with using antibiotic therapy to treat acute exacerbation of chronic bronchitis. The modified*

intent to treat group (MITT) and the modified clinically evaluable (MCE) groups will be analyzed to verify the efficacy results obtained by the applicant.

MITT population will include all treated patients enrolled EXCLUDING those who

- 1) did not have purulent pre-treatment sputum (gram stain < 25 PMN/LPF)
- 2) did not have the three AECB respiratory pathogens (*H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*) isolated from pre-treatment sputum culture
- 3) had a positive chest x-ray

MCE population will include all MITT patients EXCLUDING those who

- 4) did not have test of cure visit
- 5) were poorly compliant (received less than 4 days of study drug / <3 days for failures)
- 6) violated protocol
- 7) received another systemic antibiotic during study period

The above analysis for MITT and MCE will be done only for the subset of patients without sites 23 and 24 since we cannot confirm the validity of any data from those two sites.

[See Table 16 of Integrated Review]

### Statistical Analyses

Analyses of the pre-treatment characteristics and study medication usage for All Treated, Eligible, and Clinically Evaluable Patients by treatment group, were performed. Prognostic factors were also submitted.

### Primary Efficacy Analysis

The primary efficacy assessment was based on the analysis of clinical response in the clinically evaluable subset. Equivalence of 5-day gatifloxacin regimen to the clarithromycin regimen was determined using the 95% confidence interval (CI) around the difference in clinical cure rates (gatifloxacin – clarithromycin). The gatifloxacin 5-day regimen was considered equivalent to clarithromycin if the lower confidence limit was greater than or equal to -15%. An adjusted confidence interval, using the method described by Fleiss, was computed to take into account possible heterogeneity of response by the stratification factor, systemic corticosteroid use at randomization.

**MO COMMENT:** The lower limit of confidence at -15% was agreed upon by the FDA in reference to all submitted gatifloxacin protocols and was used in the original application.

The Fleiss method apparently calculates adjusted confidence limits based on "weighted average of the stratum-specific rate differences, where the inverse of the variance of estimated rate difference within the stratum was used as the weight for the corresponding stratum".

### Secondary Efficacy Analysis

Clinical response rates for (1) Eligible patients, and (2) All Treated Patients were tabulated. By-patient bacteriologic responses were calculated for (3) Microbiologically Evaluable Patients. Comparisons of the clinical cure rate for the (4) 5-day and (5) 7-day gatifloxacin regimens, as well as comparisons of the (6) 7-day gatifloxacin regimen to the clarithromycin regimen were considered secondary. Adjusted confidence intervals for each of these comparisons were computed as for the primary analysis. Additional secondary analyses include clinical response rates by (7) pre-treatment pathogen, (8) prognostic factor, and (9) eradication rates for primary sputum pathogens.

Relapse rates among the (10) cured Clinically Evaluable Patients who had follow-up were tabulated. The incidence of (11) new infections among All Treated Patients was compared .

**MO COMMENT:** Confidence intervals for differences in cure rates were not stratified by site although randomization was balanced by site.

## Safety

All patients who received at least one dose of study medication were evaluated for safety. The frequencies of adverse clinical events were summarized by relationship to study drug and displayed by primary term within the relevant body system, as defined in the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) adverse clinical events classification system, which was modified by BMS. Those adverse events that were considered drug related (i.e., certainly, probably or possibly drug related) were also tabulated by severity. Discontinuations due to adverse events were tabulated.

Changes in laboratory test results were tabulated by test. For patients with normal (Grade 0) pre-treatment laboratory test values, the frequencies of Grade 1, 2, 3, and 4 abnormality during/post-treatment were displayed. For each patient, the most abnormal result for each test was counted. For patients with abnormal (Grades 1, 2, or 3) pre-treatment laboratory test values, the frequencies of worsening to Grade 2, 3, or 4 abnormality during/post-treatment were displayed. For each patient, the worst grade change for each test was counted.

## Results

### **Populations**

The study period was from November 1998 to July 1999. A total of 532 patients were enrolled all in the U.S.; all but 5 patients received at least one dose of study therapy. Thirty-five sites across 22 states enrolled patients with two investigators each enrolling approximately 20% of the total number of patients. Another investigator enrolled about 15% of patients. After that, 7 investigators enrolled 3-4% of the patients, 10 investigators enrolled 1-2 % of patients and there were 15 sites which enrolled less than 1% (5 patients or less) of the patients each. Five hundred fifteen (98%) treated patients were Eligible and 468 (89%) treated patients were Clinically Evaluable. Two hundred and eleven patients (40%) were Clinically and Microbiologically Evaluable. The rates of eligibility and evaluability were fairly similar for the most part across sites. [See Tables 4A and 4B]

### **Study Sites 23 and 24 Status**

*The 35 sites that enrolled patients were from 22 different states spread out throughout the United States. Unfortunately, 37% of patients enrolled in this study were from 2 sites (site 23 and 24) both in the same state (Louisiana). Just prior to the submission of this NDA efficacy supplement, these two sites were discussed on the December 8, 2000 Teleconference between the applicant and our Division. BMS acknowledged that these two sites (Dr. Andrew DeAbate was the Principal Investigator for site 23 and a sub-investigator for site 24, while Dr. C.P. Mathew was the PI for site 24 and a sub-investigator for site 23; \_\_\_\_\_ was a sub-investigator for both sites 23 and 24) were under FDA inspection. BMS stated that an internal audit of these two investigator sites had been conducted prior to any knowledge by BMS of an Agency audit. Subsequent to learning of the Agency's audit of studies conducted by another company at these two sites, BMS hired an independent consultant to audit these two investigator sites. The consult audit apparently found no substantial issues at that time. BMS wanted to submit the sNDAs with data from these two sites integrated into the analyses. The Division stated at that time that this was acceptable, but if questions arise during the review process regarding either of these two sites, BMS may be requested to submit their analysis that excluded patients from these sites.*

*The Division reviewed the Good Clinical Practices Audit of sites 23 and 24. \_\_\_\_\_ written by \_\_\_\_\_, an independent consultant who was hired by BMS. This audit was performed on randomly selected Case Report Files of 25 patients who had been enrolled in this study. This is out of a total of 197 patients (97 patients from site 23 and 100 patients enrolled from site 24). This audit fell short of the FDA's Division of Scientific Investigation's recommendation that "...if data from Dr. DeAbate's site was to be used in support of efficacy and safety claims of any NDA, the validity and*

veracity of that data must be confirmed by an independent data audit of ALL 100% of the data generated...". Thus, in another teleconference with the applicant on March 20, 2001, the Division requested retabulation of the data without the patients from sites 23 and 24 to be submitted. Furthermore, the applicant was reassured that with timely submission of this retabulation, the original review clock should not be affected. By May 24, 2001, BMS submitted sufficient response to the request. Therefore, for the remainder of this review of study 064, the results/comments of the retabulated data (which excludes sites 23 and 24) are presented in tandem with the original submitted material (includes all the sites).

**Table 2: Gramstain quality (total samples=1250)**

# epithelial cells/LPF	5D Gatifloxacin	7D Gatifloxacin	Clarithromycin
<10	310	313	325
10-25	77	91	101
>25	12	11	10

**MO COMMENT:** Although only the presence of purulent sputum (as defined by >25 PMNs/LPF) was the criteria used for inclusion in this study, the dataset GRAMSTAIN was analyzed by this reviewer to ensure that the majority of these sputum samples also had <10 epithelial cells and that this quality of the sputum was comparable across the three arms. Out of the 1250 samples (pre-treatment samples including sites 23 and 24, most patients with duplicate specimens) of sputum, the breakdown by the number of epithelial cells in the sputum was analyzed as follows (Table 1). The three arms of study were similar with the majority of the sputum samples from enrolling patients having <10 epithelial cells/LPF.

**Table 3A: Significant Protocol Violations, All Enrolled Patients (+23/24: 56 Patients)**

Violation	Number of Patients (%)			
	Gati 5D N=175	Gati 7D N=176	Clarithro N=181	Total N=532
No test of Cure Visit	19 (9)	10 (6)	9 (5)	35 (7)
No purulent sputum pre-treatment	3 (2)	3 (2)	2 (1)	8 (2)
X-ray outside of window	—	1 (<1)	2 (1)	3 (1)
Patient did not take study drug	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Other antibiotic given	1 (<1)	1 (<1)	—	2 (<1)
X-ray evidence of pneumonia pre-tx	—	—	2 (1)	2 (<1)
Inadequate dosage	—	2 (1)	—	2 (<1)
Did not have Chronic Bronchitis	1 (<1)	—	—	1 (<1)

Few patients had more than one violation

**MO COMMENT:** As discussed earlier, sites 23 and 24 were excluded and the above data was retabulated by the applicant (see below). The number of significant protocol violations is reduced by half from 56 violations to 28. Moreover, it is interesting to note that when sites 23 and 24 are excluded, only 8 of 35 violations remain in the first category of No test of Cure Visit. In other words, 27/35 protocol violations due to no TOC visit were all coming from the two invalidated sites.

**Table 3B: Significant Protocol Violations, All Enrolled Patients (-23/24: now 28 Patients)**

Violation	Number of Patients (%)			
	Gati 5D N=110	Gati 7D N=114	Clarithro N=111	Total N=335
No test of Cure Visit	5 (5)	2 (2)	1 (<1)	8 (2)
No purulent sputum pre-treatment	3 (3)	3 (3)	2 (2)	8 (2)
X-ray outside of window	—	1 (<1)	2 (2)	3 (<1)
Patient did not take study drug	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Other antibiotic given	1 (<1)	1 (<1)	—	2 (<1)
X-ray evidence of pneumonia pre-tx	—	—	2 (1)	2 (<1)
Inadequate dosage	—	1 (<1)	—	1 (<1)
Did not have Chronic Bronchitis	1 (<1)	—	—	1 (<1)

**MO COMMENT:** Significant protocol violations were defined as those that prevented a patient from being clinically evaluable. Twenty-eight significant protocol violations occurred (Table above). There were no violations related to informed consent issues. Protocol violations were similar between the 5-day gatifloxacin, 7-day gatifloxacin, and the clarithromycin groups.

**Table 4A: Distribution of Patients in Study Population and Reasons for Exclusion (+23/24)**

Reasons (All Treated Patients)	Number of Patients (%)			
	Gati 5D N=174	Gati 7D N=175	Clarithro N=178	Total N=527
Eligible	170 (98)	171 (98)	174 (98)	515 (98)
Ineligible	4 (2)	4 (2)	4 (2)	12 (2)
No Pre-treatment purulent sputum	3 (2)	3 (2)	2 (1)	8 (2)
X-ray outside window	–	1 (<1)	2 (1)	3 (<1)
Did not have chronic bronchitis	1 (<1)	–	–	1 (<1)
Clinically Evaluable	151 (87)	154 (88)	163 (92)	468 (89)
Clinically Unevaluable	23 (13)	21 (12)	15 (8)	59 (11)
No Test of Cure Visit	16 (9)	11 (6)	9 (5)	36 (7)
Ineligible	4 (2)	4 (2)	4 (2)	12 (2)
Insufficient dosage	2 (1)	5 (3)	2 (1)	9 (2)
Other antibiotic received	1 (<1)	1 (<1)	–	2 (<1)
Microbiologically Evaluable Patients	70 (40)	65 (37)	76 (43)	211 (40)

Eighty-nine % of the All Treated Patients were evaluable and 59 patients (11%) were clinically unevaluable, the major reason being no post-treatment clinical evaluation within the acceptable window. Three hundred and ten (59%) of the All Treated Patients had a pre-treatment pathogen and a majority (281 or 53%) (281 or 53%) were Clinically Evaluable. Forty percent of treated patients were Microbiologically Evaluable. This difference from the Clinically Evaluable patient numbers was due the pathogens isolated at pre-treatment that were resistant to clarithromycin.

**MO COMMENT:** Patients were balanced between the 3 groups in terms of eligibility, clinical evaluability, and microbiological evaluability. They were also balanced in terms of reasons for ineligibility and unevaluability. Each of the three arms had a similar frequency of patients with clarithromycin resistant pathogens. Except: Almost double the numbers (16 for 5-day gatifloxacin arm vs. 9 for clarithromycin arm) for the clinically unevaluable reason "No test of cure visit".

Again, sites 23 and 24 were excluded and the above Table retabulated as follows.

**Table 4B: Distribution of Patients in Study Population and Reasons for Exclusion (-23/24)**

Reasons (All Treated Patients)	Number of Patients (%)			
	Gati 5D N=109	Gati 7D N=113	Clarithro N=108	Total N=330
Eligible	105(96)	109 (96)	104 (96)	318 (96)
Ineligible	4 (4)	4 (4)	4 (4)	12 (4)
No Pre-treatment purulent sputum	3 (3)	3 (3)	2 (2)	8 (2)
X-ray outside window	–	1 (<1)	2 (2)	3 (<1)
Did not have chronic bronchitis	1 (<1)	–	–	1 (<1)
Clinically Evaluable	97 (89)	102 (90)	101 (94)	300 (91)
Clinically Unevaluable	12 (11)	11 (10)	7 (6)	30 (9)
No Test of Cure Visit	5 (5)	3 (3)	1 (<1)	9 (3)
Ineligible	4 (4)	4 (4)	4 (4)	12 (4)
Insufficient dosage	2 (2)	3 (3)	2 (2)	7 (2)
Other antibiotic received	1 (<1)	1 (<1)	–	2 (<1)
Microbiologically Evaluable Patients	43 (39)	43 (38)	41 (38)	127 (38)

**MO COMMENT:** Even when sites 23 and 24 are removed from analysis (37% of the patients removed) of All Treated Patients, the three groups are balanced and comparable in regards to the reasons for ineligibility and clinical unevaluability.

**Data Sets**

The safety data set consisted of All Treated Patients.

The primary data set for analysis of clinical efficacy consisted of the Clinically Evaluable Patients; the primary data set for analysis of bacteriologic efficacy consisted of the Microbiologically Evaluable Patients.

**Demography and Patient Characteristics**

Of the 527 patients treated, 54% were male; the majority (80%) was white and the median age was 45 years (Table below). The demographics in the 5-day gatifloxacin treated patients were similar to the 7-day gatifloxacin treated and clarithromycin-treated patients.

**Table 5A: Demography, All Treated Patients (+23/24)**

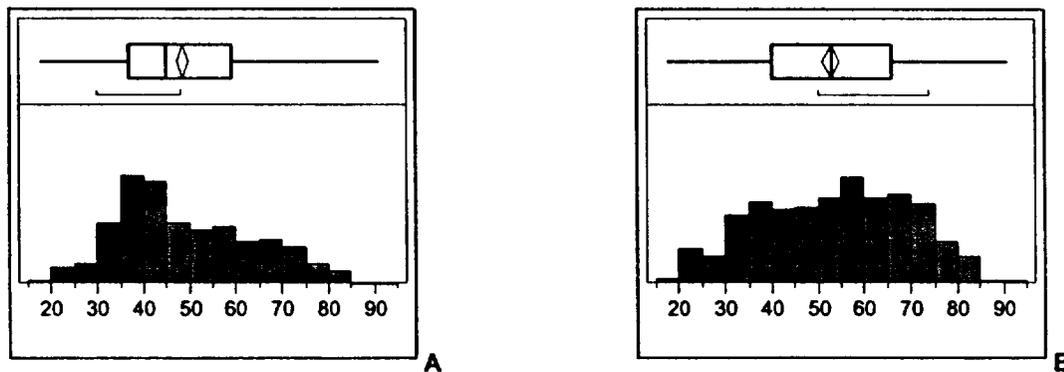
Characteristic	Number of Patients (%)			
	Gati 5D N = 174	Gati 7D N = 175	Clarithro 10 D N = 178	Total N = 527
<b>Gender [N (%)]:</b>				
Male	101 (58)	86 (49)	97 (54)	284 (54)
Female	73 (42)	89 (51)	81 (46)	243 (46)
<b>Race [N(%)]:</b>				
White	109 (63)	112 (64)	103 (58)	324 (61)
Black	61 (35)	57 (33)	72 (40)	190 (36)
Hispanic	4 (2)	4 (2)	2 (1)	10 (2)
Other <sup>a</sup>	--	2 (1)	1 (<1)	3 (1)
<b>Age (years):</b>				
Mean	48	48	48	48
Median	46	45	44.5	45
Min - Max	18 - 84	21-91	22 - 86	18-91
<b>Weight<sup>b</sup> (kg):</b>				
Mean	79.4	80.7	79.8	80.0
Median	75.1	77.1	77.1	76.7
Min - Max	40.8 - 143.3	36.7 - 154.2	40.8 - 154.2	36.7 - 154.2

**MO COMMENT:** The demographic characteristics in the two arms are similar for All Treated Patients, Eligible Patients, and Clinically Evaluable Patients. Of the 527 patients treated, 54% were male,

61% white, and the median age was 45 years for All Treated Patients. Looking at the distribution in age graphically (Figure 1, panel A), the majority of patients are less than 60 years of age and there is a large number of patients clustered around the median age of 45 years.

Demographic characteristics were retabulated without the patients from sites 23 and 24 (Table below). The demographic picture DOES CHANGE without those two sites. There are less men (46% down from 54%), less black patients (10% down from 36%), and older age (median age now at 53 years up from 45 years). Looking at the age parameter graphically (Figure 1, panel B), the ages of the patients are now more evenly distributed with the shift of cluster of patients around 60 years of age. Thus, it appears that patients from sites 23 and 24 were mainly male, black, and younger in age.

**Figure 1: Panel A depicts distribution of age for All Treated Patients  
Panel B depicts distribution of age for All Treated Patients without sites 23 & 24**



**Table 5B: Demography, All Treated Patients (-23/24)**

Characteristic	Number of Patients (%)			
	Gati 5D N = 109	Gati 7D N = 113	Clarithro 10 D N = 108	Total N = 330
<b>Gender [N (%)]:</b>				
Male	58 (53)	47 (42)	48 (44)	153 (46)
Female	51 (47)	66 (58)	60 (56)	177 (54)
<b>Race [N(%)]:</b>				
White	98 (90)	95 (84)	92 (85)	285 (86)
Black	8 (7)	12 (11)	14 (13)	34 (10)
Hispanic	3 (3)	4 (4)	2 (2)	9 (3)
Other <sup>a</sup>	--	2 (1)	--	2 (1)
<b>Age (years):</b>				
Mean	52	53	54	53
Median	51	54	55	53
Min - Max	18 - 84	21-91	22 - 86	18-91
<b>Weight<sup>b</sup> (kg):</b>				

Mean	80.5	81.8	84.7	82.3
Median	79.4	77.4	82.1	79.4
Min - Max	40.8 – 143.3	36.7 – 154.2	42.4 – 154.2	36.7 – 154.2

**Medical History and Presenting Conditions**

A wide array of conditions was recorded for medical history with most systems represented. One patient (028-172) who was listed under protocol violations was not producing sputum for the required three consecutive months for at least two consecutive years and therefore did not meet the definition of chronic bronchitis for the purpose of this study. Otherwise, all other treated patients had a history of chronic bronchitis that met the definition of chronic cough and sputum production on most days for 3 consecutive months for greater than two consecutive years. A variety of other respiratory conditions were represented as well, including asthma/asthmatic bronchitis in a quarter of the patients and COPD /emphysema is 41% of the patients. The incidence of asthma at 24% and COPD at 46% was somewhat higher in the clarithromycin arm over the gatifloxacin arm (18% for asthma and 40% for COPD). This slight imbalance contributed to the overall difference of 66% (114/174 patients) underlying respiratory conditions totaled in the gatifloxacin 5 D group verses 75% (134/178) in the clarithromycin group.

The number of episodes of AECB that the patients had experienced in the previous 12 months was similar between the two treatment groups; the majority (69%) had 2 or 3 episodes during the previous year.

Within five days of the pre-treatment visit, there were no patients that received any systemic antimicrobials. Corticosteroids were used in 8 % (41/527) of the patients at the time of randomization. Prednisone was the predominant systemic corticosteroid used (7-8% of the patients in each treatment arm).

At entry, all patients in the three arms had increased sputum production and increased cough. Increased purulent sputum was reported in 99% of the patients in all three treatment arms. The three treatment arms were comparable in the incidence of increased dyspnea.

**Table 6A: Incidence of Dyspnea, All Treated Patients (+23/24)**

Signs/symptoms	Number of Patients (%)			
	Gati 5D: N=174	Gati 7D: N=175	Clarithro N=178	Total: N=527
Increased dyspnea	144 (83)	143 (82)	151 (85)	438 (83)

Moreover, the majority of patient also presented with additional signs and symptoms associated with acute exacerbation of chronic bronchitis including chest tightness, malaise, and headache. There were no appreciable differences between the three treatment groups.

*MO COMMENT: The representation of different medical conditions was adequate and well balanced between the 2 groups except for underlying respiratory conditions. More patients were listed in the clarithromycin group as compared to the gatifloxacin 5 day group. This actually goes to the heart of how "sick" these patients are at baseline. Also of note is that the application does not breakdown the non-antimicrobial medications which the patients are maintained on at study entry. For example, we are given how many patients have a medical history of asthma for example, but we do not have a measure of what that means i.e. how many are on chronic bronchodilators, systemic asthma medications, etc.*

*Sites 23 and 24 were removed and the medical history of all treated patients retabulated. Again, a wide array of conditions was recorded for medical history with most systems represented. Except for that one patient already discussed above in the 5-day gatifloxacin arm, all other treated patients had a history of chronic bronchitis that met the definition of chronic cough and sputum production on most days for 3 consecutive months for greater than two consecutive years. A variety of other respiratory conditions were represented as well, including asthma/asthmatic bronchitis in a quarter of the patients and COPD /emphysema is 33% of the patients. This time, the incidence of asthma was highest for the 7-day gatifloxacin*

group at 34% as compared to 19% for the 5-day gatifloxacin group. It was 27% for clarithromycin arm. This slight imbalance contributed to the overall difference of 81.4 % (92/113) underlying respiratory conditions totaled in the 7-day gatifloxacin group versus 63.3 % (69/109) for the 5-day gatifloxacin group and 70% (76/108) in the clarithromycin group. The number of episodes of AEBC that the patients had experienced in the previous 12 months was similar between the two treatment groups; the majority (57%) had 2 or 3 episodes during the previous year.

Within five days of the pre-treatment visit, there were no patients that received any systemic antimicrobials. Corticosteroids were used in 12 % (41/330) of the patients at the time of randomization. Prednisone was the predominant systemic corticosteroid used (11-14% of the patients in each treatment arm).

At entry, all patients (100%) in the three arms had increase sputum production and increased cough. Increased purulent sputum was reported in 98-99% of the patients in all 3 treatment arms. The three treatment arms were comparable in the incidence of increased dyspnea as follows.

**Table 6B: Incidence of Dyspnea – All Treated Patients (-23/24)**

Signs/symptoms	Number of Patients (%)			
	Gati 5D: N=109	Gati 7D: N=113	Clarithro N=108	Total: N=330
Increased dyspnea	95 (87)	99 (88)	97 (90)	291 (88)

Moreover, the majority of patient also presented with additional signs and symptoms associated with acute exacerbation of chronic bronchitis including chest tightness, malaise, and headache. There were no appreciable differences between the three treatment groups.

It is interesting to note that the number of patients using systemic steroid therapy at the time of entry does not change when site 23 and 24 patients are removed (41/527 to 41/330). Not one patient from sites 23 and 24 was using systemic steroids at entry. Thus, the DEMOGRAPHIC differences between the two sets of patients (original versus without sites 23 and 24) paint a picture of patients in sites 23 and 24 to be younger, less respiratory compromised at baseline, black, and male.

**Microbiologic Documentation**

A total of 428 pathogens were isolated from 310 (59%) to the All Treated patients. Two-hundred and thirteen patients had a single pathogen, while 97 had multiple pathogens. There were 63 isolates of *H. influenzae*, 49 isolates of *M. catarrhalis*, and 47 of *S. pneumoniae*. Of the *H. influenzae* isolates, there were 17 (24%) were  $\beta$ -lactamase positive. There were 10 (21% of total) penicillin intermediate *S. pneumoniae*. There were no penicillin resistant *S. pneumoniae* isolated. Other frequently isolated respiratory organisms included *S. aureus* (94) and *H. parainfluenzae* (43). *P. aeruginosa* was isolated only once in the 5-day gatifloxacin arm compared to nine in the 7-day gatifloxacin group and seven in the clarithromycin arms. There were no isolates resistant to gatifloxacin whereas 144 (34%) pre-treatment isolates were resistant to clarithromycin.

**MO COMMENT:** The 3 major pathogens usually involved in AEBC (*H. influenzae*, *S. pneumoniae* and *M. catarrhalis*) are well represented in the study. There was also a good proportion of patients with *H. parainfluenzae* and *S. aureus* to allow for assessment of efficacy against those organisms. Generally, each treatment group had comparable numbers of the pathogens in question.

Removing sites 23 and 24 from the tabulations resulted in proportionately similar numbers of patients with specific pathogens and did not change the overall comparability of the three treatment arms.

**Table 7: Microbiological Status – Percent of Original Patients Left (- 23/ 24)**

	Original Number	Without sites 23 & 24	% of Original Number
# of All Treated Pts	N=527	N=330	63%
Pts with pathogen	N=310	N=191	62%
<b>Total # of pathogens</b>			
<i>H. influenzae</i>	N=63	N=35	56%
<i>M. catarrhalis</i>	N=49	N=34	69%
<i>S. pneumoniae</i>	N=47	N=28	60%
<i>H. parainfluenzae</i>	N=43	N=24	56%
<i>S. aureus</i>	N=94	N=51	54%

**Prognostic Factors, All Treated Patients**

Eighty-two percent of the All Treated Patients had Type I exacerbation by Anthonisen criteria, and the remainder had Type II exacerbation. The one exception was a patient in the 5-day gatifloxacin arm (026-146) who had a Type III exacerbation with only 2 signs and symptoms associated with AECB by the Anthonisen criterion and as defined by the study inclusion criteria. At the time of randomization, the median duration of the current episode of exacerbation prior to enrollment was six days for all three arms, and in 86% of the patients, the current episode was less than fifteen days in duration. Forty-one patients (8%) were receiving systemic corticosteroids at the time of randomization with similar frequencies in all three arms. Three hundred and forty-eight (66%) of the All Treated Patients were smokers or had stopped smoking within the two months before study, and 88% had a history of smoking. The number of patients in the three groups was comparable.

*MO COMMENT: The three groups were generally similar in terms of exacerbation type, smoking history, current smoking status, duration of current episode of AECB, and pre-treatment systemic corticosteroid use.*

*Removing sites 23 and 24 from the tabulations resulted in proportionately similar numbers of patients for each of the specific prognostic factors and did not change the overall comparability of the three treatment arms. The two exception were systemic corticosteroid use at entry (discussed above under medical conditions) and current smoking status. The percent of patients with systemic corticosteroid use in the retabulated group increases from 8% to 12% since not one patient from sites 23 and 24 were using systemic steroids at study entry. It appears that there were more current smokers in sites 23 and 24. The percent of current smokers decreases from 66% in the original All Treated Patients to 48% in the retabulated group without sites 23 and 24.*

*Thus, the patient population of sites 23 and 24 are more younger, more male, more black, more current smokers, and are less respiratory compromised at baseline.*

**Table 8: Prognostic Factors – Percent of Original Patients Left (- 23/24)**

	Original Number	Without sites 23 & 24	% of original
# of All Treated Pts	N=527	N=330	63%
Exacerbation Type I	N=434	N=287	66%
Current duration <15 d	N=451	N=256	57%
Corticosteroid use	N=41	N=41	100%
Current smoker	N=348	N=157	45%
Has Smoking history	N=465	N=271	58%

**Study Therapy**

The majority of patients (89%) received 10 days (20 doses) of therapy. Duration of less than 10 days occurred in 8 (5%) gatifloxacin 5-day arm, 10 (6%) gatifloxacin 7-day arm, and 9 (5%) of the clarithromycin treated patients. A total of 15 (3%) patients were lost to follow-up and thus the total dosing unknown. There were 6 (3%) in the 5-day gatifloxacin group, 4 (2%) in the 7-day gatifloxacin group, and 5 (3%) in the clarithromycin group for whom the total dosing was unknown. A total of 19 (4%) patients discontinued study therapy prematurely, with 2% of patients discontinuing in the 5-day gatifloxacin arm, 3% discontinuing in the clarithromycin arm, and 5% discontinuing in the 7-day gatifloxacin arm. Ten patients discontinued medication due to adverse events. Six discontinued due to non-qualifying Gram stain (PMN Not greater than 25/LPF). Two discontinued due to noncompliance; and one patient lost her medication. There were no interruptions of therapy related to clinical findings or laboratory abnormalities that occurred on therapy.

*MO COMMENTS: CRFs of patients receiving less than 8 days of study drug reviewed. Review of the specific crfs for the identified patients below concurred with the applicant's assessments.  
 5-day gatifloxacin: 051-553, 031-363, 037-254, 024-753, 027-160  
 7-day gatifloxacin: 010-279, 014-830, 023-846, 041-735, 049-519, 013-470, 031-370, 041-622, 023-696, 050-583*

10-day clarithromycin: 009-055, 010-277, 027-161, 007-046, and 041-734

Removing sites 23 and 24 from the tabulations resulted in proportionately similar numbers of patients with 20 doses of study medication taken and did not change the overall comparability of the three treatment arms. However, it is interesting to note that the majority (13/15) of "dosing unknown due to being lost to follow-up" patients was from sites 23 and 24.

**Table 9: Study Drug Exposure - Percent of Original Patients Left (-23/24)**

Study drug exposure	Original Number	Without sites 23 & 24	% of original
# of All Treated Pts	N=527	N=330	63%
Pts with 20 doses taken	N=467	N=290	62%
Pts with <8 days taken	N=20	N=17	85%
Dosing unknown	N=15	N=2	13%

**Concomitant Therapy**

A total of 10 (2%) patients used concomitant antimicrobial medications. One patient in the 5-day gatifloxacin arm received a systemic concomitant antibacterial, amoxicillin/clavulanate, on Day 10 for treatment of chronic bronchitis prior to completing his last dose of gatifloxacin. Systemic antivirals were given for occurrences of herpes (in a patient on 5-day gatifloxacin arm) and shingles (in a patient on 7-day gatifloxacin arm). The remaining 7 patients used topical antimicrobial agents (acyclovir, nystatin, clotrimazole, ketoconazole, dexamethasone/neomycin/polymixin B). Fifty (9%) of All Treated Patients received concomitant systemic corticosteroids with the use comparable in the three treatment groups. Of these, 49 received prednisone, two patients received methylprednisolone, and one patient received cortisone. A total of 299 (57%) patients received a variety of concomitant non-antimicrobial medications. Antibronchospastics/antiasthmatics at 30%, cardiac medications at 25%, and analgesics at 20%, and non-systemic corticosteroids at 17% were the most frequently used medications. The use of these medications was generally comparable in the three treatment arms. Non-drug therapy use was in 33 (6%) of patients and mainly consisted of supplemental oxygen administration in 27 (5%).

**MO COMMENT:** It is interesting to note that although this original population of patients enrolled to 064 study included over 85% of patients who were Type I Anthonisen exacerbation type (and thus denoting "moderate to severe" cases of underlying chronic bronchitic disease) AND the patients were being enrolled to the study due to acute illness, only 9% used concomitant systemic steroids, 17% used non-systemic steroids, and 30% used antibronchospastic/antiasthmatic drugs. This makes the reviewer wonder how "moderate-to-severe" the underlying respiratory diseases were in these patients.

Removing sites 23 and 24 from the tabulations resulted in disproportionate numbers of patients taking different types of concomitant medications. It appears that much fewer patients in sites 23 and 24 were taking other concomitant medications (no one taking other antimicrobials, no one taking systemic corticosteroids, and few numbers taking non-antimicrobials) compared to all the other sites as a whole.

**Table 10: Concomitant Drugs -Percent of Original Patients Left (-23/24)**

Concomitant Drugs	Original Number	Without sites 23 & 24	% of Original Left
# of All Treated Pts	N=527	N=330	63%
Other antimicrobials	N=10	N=10	100%
Systemic Corticosteroids	N=50	N=50	100%
Non-antimicrobials	N=299	N=250	84%
Antibronchospastic/ antiasthmatics	N=159	N=145	91%
Cardiac medications	N=134	N=119	89%
Analgesics	N=106	N=99	93%
Non-systemic steroids	N=90	N=89	99%

**Post-treatment Therapy**

The 65 patients who received systemic antibacterial agents post-treatment (5-day gatifloxacin: 23, 7-day gatifloxacin: 20, and clarithromycin:22) fell into four main groups.

- 1) Treatment failures who received an alternate antibiotic for AECB: (5-day gatifloxacin: 15, 7-day gatifloxacin:12, clarithromycin:15)
- 2) Patients who were treated for new infections: 4 patients in the 5-day gatifloxacin arm, 5 in the 7-day gatifloxacin arm, and 3 patients in the clarithromycin arm
- 3) Patients who discontinued study therapy early due to an adverse event: 2 patients in the 5-day gatifloxacin arm, 2 in the 7-day gatifloxacin arm, and one patient in the clarithromycin arm
- 4) Patients who were cured at TOC visit and relapsed: 2 patients in the 5-day gatifloxacin arm , 1 in the 7-day gatifloxacin arm, and 3 patients in the clarithromycin arm.

Systemic antimicrobials were prescribed with similar frequency in the three treatment arms with Amoxicillin/clavulanate as the most frequent B-Lactam and Ciprofloxacin as the most frequent quinolone post-treatment (9/21 receiving quinolones). There were five patients who received clarithromycin. For systemic antiviral medications, one patient in the 5-day gatifloxacin arm took acyclovir for herpes simplex infection and another patient in the 7-day gatifloxacin arm took famciclovir for shingles. Fluconazole taken by one patient in the 5-day gatifloxacin group constituted the only systemic antifungal medication. There were 11 incidences of non-systemic topical antimicrobial usage in total with comparable distribution between the three arms of study.

Fifty (9%) patients received a post-treatment systemic corticosteroid. Forty-five of these received prednisone and seven received methylprednisolone. The majority of these patients (43/50) were continuing their prednisone therapy from concomitant use. Non-antimicrobial medications used in post-treatment paralleled concomitant use with 304 (58%) making up this population.

*MO COMMENT: Similar numbers of patients in the three arms went on to use antimicrobial therapy post-treatment from the study. Of note, broad-spectrum antibiotic therapy through this protocol did not decrease systemic or non-systemic corticosteroid usage. The post-treatment usage of antibronchospastic/antiasthmatic drugs did not lessen either. Removing sites 23 and 24 from the tabulations resulted in disproportionate numbers of patients taking post-study drugs. It appears that much fewer patients in sites 23 and 24 went on to take post-treatment medications whether it be systemic or non-systemic antimicrobials, systemic corticosteroids, or non-antimicrobials including non-systemic steroids and other respiratory medications.*

**Table 11: Post Treatment Drugs -Percent of Original Patients Left (-23/24)**

Post-treatment Drugs	Original Number	Without sites 23 & 24	% of original
# of All Treated Pts	N=527	N=330	63%
Systemic Antimicrobials	N=68	N=51	75%
Non-systemic Antimicrobials	N=11	N=11	100%
Systemic Corticosteroids	N=50	N=50	100%
Non-antimicrobials	N=304	N=252	83%
Antibronchospastic/ antiasthmatics	N=164	N=148	90%
Cardiac medications	N=137	N=121	88%
Analgesics	N=107	N=101	94%
Non-systemic corticosteroids	N=97	N=96	99%

*Several overall conclusions are reachable regarding the study population characteristics. Although the majority of patients enrolled were categorized as Anthonisen Type I and thus expected to be quite ill ("moderate to severe") with an acute exacerbation of chronic bronchitis, a large body of supportive*

evidence say otherwise. The majority of enrolled patients were less than 60 years with the median at 45 years. A very small percentage of patients were using systemic corticosteroids at entry and likewise small numbers were using oxygen therapy. Only a minority of patients were using concomitant anibronchospastic/antiasthmatic medications and even fewer number of patients were using concomitant inhalant corticosteroid therapy. Taking these observations a step further, the subset of patients enrolled from sites 23 and 24 seem to be even farther away from the picture of AECEB patients we would consider with "moderate to severe" baseline disease. Compared to the original All Treated patients, the subset of patients from sites 23 and 24 were proportionally more younger, more current smokers, less likely to be taking respiratory medications or oxygen therapy at baseline. This subset also had more male, more black, and more smoking patients.

**Efficacy Results**

**MO COMMENT:** Appendix 4 of this sNDA volume 4 gives 42 instances where the Investigator's evaluation of clinical response differed from the Medical Monitors. More discrepancies were listed for the gatifloxacin arms over the clarithromycin arm. However, the proportions of patients being reassigned were similar (majority from Unable to Determine by the investigators to Cured by the Medical Monitor). There were 14 discrepancies in the 5-day gatifloxacin arm, 19 in the 7-day gatifloxacin arm, and 9 in the clarithromycin arm with breakdown as follows:

**Table 12A: Discrepancies in Response Reassigned**

Clinical response reassigned By BMS Medical Monitor	5-day Gatifloxacin Discrepancies (n=14)	7-day Gatifloxacin Discrepancies (n=19)	Clarithromycin Discrepancies (n=9)
From UTD to Cured	11 patients	12 patients	8 patients
From UTD to Failure	3	4	1
From Cure to Failure	--	3	--

Sites 23 and 24 accounted for 6 of the 14 discrepancies in the 5-day gatifloxacin arm, 7/19 in the 7-day gatifloxacin arm and 4/8 in the clarithromycin arm. Taking out these contributors, the data is retabulated as follows:

**Table 12B: Discrepancies in Response Reassigned (-23/24)**

Clinical response reassigned By BMS Medical Monitor	5-day Gatifloxacin Discrepancies (n=8)	7-day Gatifloxacin Discrepancies (n=12)	Clarithromycin Discrepancies (n=5)
From UTD to Cured	5 patients	7 patients	4 patients
From UTD to Failure	2	2	1
From Cure to Failure	1	3	--

Although patients were randomized according to corticosteroid use, confidence intervals were constructed only for the group as a whole and adjusted for the corticosteroid stratification using the Fleiss method. (This method was verified by the review team statistician: Dr. Nancy Silliman). The primary efficacy analysis was not done on an intent-to-treat basis; patients who discontinued study drug before receiving 5 days of therapy because of adverse events or worsening of their condition were not considered evaluable and thus were not included in the primary efficacy analysis. The patients were well balanced between the two study groups. The intent-to-treat population would be more closely represented by the All Treated of the Eligible subsets. Thus, the FDA will consider analyses of all subsets. As discussed above under Datasets section, the applicants efficacy results will be verified by the reviewer with MITT population and MCE population excluding sites 23 and 24 (will be presented in the integrated analysis review).

**Clinical Response; Clinically Evaluable Patients**

Cure rates were similar in the three treatment groups as per the applicant's analysis. 95 % Confidence Intervals for Difference in Cure Rates:

- 1) Primary comparison: 5-day gatifloxacin to 10-day clarithromycin (-6.1%, 7.0%)
- 2) 5-day gatifloxacin compared to 7-day gatifloxacin (-5.5%, 8.0%)
- 3) 7-day gatifloxacin vs 10-day clarithromycin (-8.9%, 5.0%)

**Table 13A: Clinical Response, Clinically Evaluable Patients (Applicant's Analysis +23/24)**

Clinical Response	Number of Patients (%)			
	Gati 5D (N=151)	Gati 7D (N=154)	Claritho (N=163)	Total (N=468)
Cure	135 (89)	136 (88)	145 (89)	416 (89)
Failure	16 (11)	18 (12)	18 (11)	52 (11)

**MO COMMENT:** The cure rate overall in the clinically evaluable patient population (applicant's primary efficacy analysis) was similar across the three treatment arms. The lower limit of the 95% CI for this analysis is within the designated limit of 15% for all three comparisons.

The breakdown of clinically evaluable patients by site showed comparable cure rates between the three treatment arms.

Removing sites 23 and 24 from the tabulations did not change the cure rates in the three arms to a significant degree. Cure rates were similar in the three treatment groups as per the applicant's analysis and the lower limit of the 95% CI within the designated limit of 15% for all three comparisons.

95 % Confidence Intervals for Difference in Cure Rates:

- 1) Primary comparison: 5-day gatifloxacin to 10-day clarithromycin (-5.3 %, 12.3 %)
- 2) 5-day gatifloxacin compared to 7-day gatifloxacin (-4.4 %, 13.6 %)
- 3) 7-day gatifloxacin vs 10-day clarithromycin (-12.7 %, 6.9 %)

**Table 13B: Clinical Response, Clinically Evaluable Patients (-23/24) (Applicant's analysis)**

Clinical Response	Number of Patients (%)			
	Gati 5D (N=97)	Gati 7D (N=102)	Claritho (N=101)	Total (N=300)
Cure	86 (89)	86 (84)	86 (85)	258 (86)
Failure	11 (11)	16 (16)	15 (15)	42 (14)

**Clinical Response; Eligible and All Treated Patients**

**Table 14A: Clinical Response, Clinically Eligible Patients (Applicant's analysis)**

Clinical Response	Number of Patients (%)			
	Gati 5D (N=170)	Gati 7D (N=171)	Claritho (N=174)	Total (N=515)
Cure	141 (86)	147 (86)	151 (87)	445 (86)
Failure	29 (14)	24 (14)	23 (13)	70 (14)

95% CI for 5-day gatifloxacin vs. clarithromycin (-7.7%, 6.4%)

95% CI for 5-day gatifloxacin vs. 7-day gatifloxacin (-6.9%, 7.5%)

95% CI for 7-day gatifloxacin vs. clarithromycin (-9.2%, 5.2%)

**Table 15A: Clinical Response, All Treated Patients (Applicant's Analysis)**

Clinical Response	Number of Patients (%)			
	Gati 5D (N=174)	Gati 7D (N=175)	Claritho (N=178)	Total (N=527)
Cure	149 (86)	149 (85)	154 (87)	452 (86)
Failure	25 (14)	26 (15)	24 (13)	75 (14)

95% CI for 5-day gatifloxacin vs. clarithromycin (-8.4%, 5.8%)  
 95% CI for 5-day gatifloxacin vs. 7-day gatifloxacin (-7.1%, 7.5%)  
 95% CI for 7-day gatifloxacin vs. clarithromycin (-9.8%, 4.7%)

**MO COMMENT:** The cure rates by study site for the Eligible Population was similar to the site distribution seen with Clinically Evaluable Patients as discussed above. The lower limits of these two analyses were also within the designated limit of -15%.

Removing sites 23 and 24 from the tabulations did not change the cure rates in the three arms to a significant degree. Cure rates were similar in the three treatment groups as per the applicant's analysis and the lower limit of the 95% CI within the designated limit of 15% for all three comparisons.

**Table 14B: Clinical Response, Eligible Patients(-23/24) (Applicant's Analysis)**

Clinical Response	Number of Patients (%)			
	Gati 5D (N=105)	Gati 7D (N=109)	Claritho (N=104)	Total (N=318)
Cure	92 (88)	92 (84)	88 (85)	272 (86)
Failure	13 (12)	17 (16)	16 (15)	46 (14)

95% CI for 5-day gatifloxacin vs. clarithromycin (-6.3%, 11.6%)  
 95% CI for 5-day gatifloxacin vs. 7-day gatifloxacin (-5.7%, 12.1%)  
 95% CI for 7-day gatifloxacin vs. clarithromycin (-11.9%, 7.5%)

**Table 15B: Clinical Response, All Treated Patients (-23/24) (Applicant's Analysis)**

Clinical Response	Number of Patients (%)			
	Gati 5D (N=109)	Gati 7D (N=113)	Claritho (N=108)	Total (N=330)*
Cure	94 (86)	94 (83)	91 (84)	279 (85)
Failure	13 (12)	18 (16)	16 (15)	47 (14)

\* There are 4 patients total who were Unable to Determine  
 95% CI for 5-day gatifloxacin vs. clarithromycin (-7.8%, 10.5%)  
 95% CI for 5-day gatifloxacin vs. 7-day gatifloxacin (-6.4%, 11.9%)  
 95% CI for 7-day gatifloxacin vs. clarithromycin (-12.7%, 6.8%)

**APPEARS THIS WAY  
 ON ORIGINAL**

**Table 16A: Clinical Response by Prognostic Factor; Clinically Evaluable Patients (+23/24)**

Prognostic Factor/ Subcategory	Number Cured/Evaluable Patients (%)		
	Gatifloxacin 5D N = 151	Gatifloxacin 7D N = 154	Clarithromycin N = 163
<u>Exacerbation type</u>			
Type I	111/124 (90)	110/127 (87)	118/136 (87)
Type II	23/26 (88)	26/27 (96)	27/27 (100)
Type III	1/1 (100)	--	--
<u>Duration of Current Episode</u>			
0 - 7 Days	86/101 (85)	98/110 (89)	102/109 (94)
> 7 Days	48/49 (98)	36/40 (90)	43/54 (80)
Not Recorded	1/1 (100)	2/4 (50)	--
<u>Systemic Corticosteroid</u>			
<u>Use at Randomization</u>			
Yes	9/14 (64)	10/12 (83)	11/14 (79)
No	126/137 (92)	126/142 (89)	134/149 (90)
<u>Current Smoking Status</u>			
Smoker	94/101 (93)	94/99 (95)	97/107 (91)
Non-Smoker	41/50 (82)	42/55 (76)	48/56 (86)
<u>History of Smoking</u>			
Yes	120/134 (90)	123/137 (90)	130/144 (90)
No	15/17 (88)	13/17 (76)	15/19 (79)

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 16B: Clinical Response by Prognostic Factor; Clinically Evaluable Patients (-23/24)**

Prognostic Factor/ Subcategory	Number Cured/Evaluable Patients (%)		
	Gatifloxacin 5D N = 97	Gatifloxacin 7D N = 102	Clarithromycin N = 101
<u>Exacerbation type</u>			
Type I	74/83 (89)	74/89 (83)	73/88 (83)
Type II	11/13 (85)	12/13 (92)	13/13 (100)
Type III	1/1 (100)	--	--
<u>Duration of Current Episode</u>			
0 - 7 Days	41/51 (80)	51/61 (84)	50/54 (93)
> 7 Days	44/45 (98)	33/37 (89)	36/47 (77)
Not Recorded	1/1 (100)	2/4 (50)	--
<u>Systemic Corticosteroid Use at Randomization</u>			
Yes	9/14 (64)	10/12 (83)	11/14 (79)
No	77/83 (93)	76/90 (84)	75/87 (86)
<u>Current Smoking Status</u>			
Smoker	46/49 (94)	44/48 (92)	40/47 (85)
Non-Smoker	40/48 (83)	42/54 (78)	46/54 (85)
<u>History of Smoking</u>			
Yes	72/81 (89)	73/85 (86)	72/83 (87)
No	14/16 (88)	13/17 (76)	14/18 (78)

**MO COMMENT:** Cure Rates in clinically evaluable patients between the three arms for the above relevant prognostic factors were generally comparable with or without the inclusion of data from sites 23/24. The cure rate for patients with Type I exacerbation was similar in the 5-day gatifloxacin arm to the other two treatment regimens. However, for patients presenting with symptoms less than 7 days, the clarithromycin arm numerically does better, while for patients presenting with symptoms greater than 7 days, the 5-day gatifloxacin arm had a numerically better cure rate over the comparators. It is hard to make sense of these results. What makes more sense is that patients who were on pre-treatment corticosteroids had worse cure rates than patients not on corticosteroids across the three arms. The issue of smokers having better cure rate than non-smoker subjects is seen in this efficacy supplement results as was seen in the original NDA. Patients who were current smokers as well as patients who had a history of smoking fared better across all three arms with an overall cure rate of 93% for current smokers versus 81% cure rate for current non-smokers (90 % versus 82% without sites 23/24). The Company was asked to supply us with a closer look at the distribution of smokers and non-smokers with respect to age, race, gender, history of asthma, use of other drugs concomitantly, i.e. Beta adrenergics, anticholinergics, corticosteroids, and the presence of one of the 5 major pathogens isolated. The results provided in June 26, 2001 submission are summarized and shown in table 17 below.

**Table 17: Study-064 (+23/24): Demography by Current Smoking Status, All Treated Patients**

	Gatifloxacin 5 day		Gatifloxacin 7days		Clarithromycin		Total	
<b>Age &lt;65 Years</b>	yes	no	yes	no	yes	no	yes	no
	113	31	109	36	111	35	333	102
	118	56	111	64	119	59	348	179
	96%	55%	98%	56%	93%	59%	96%	57%
<b>Race (Black)*</b>	yes	no	yes	no	yes	no	yes	no
	55	6	50	7	66	6	172	19
	118	56	111	64	119	59	348	179
	47%	11%	45%	11%	55%	10%	49%	11%
<b>Gender (female)</b>	yes	no	yes	no	yes	no	yes	no
	46	27	56	33	48	33	150	93
	118	56	111	64	119	59	348	179
	39%	48%	52%	52%	40%	56%	43%	52%
<b>Numbers of three** Relevant pathogens</b>	yes	no	yes	no	yes	no	yes	no
	35	19	31	17	36	17	102	53
	118	56	111	64	119	59	348	179
	30%	34%	28%	26%	30%	29%	29%	30%
<b>Concomitant Inhaled Steroids</b>	yes	no	yes	no	yes	no	yes	no
	6	13	7	20	9	24	22	57
	118	56	111	64	119	59	348	179
	5%	23%	6%	31%	8%	41%	6%	32%
<b>Concomitant Systemic steroids</b>	yes	no	yes	no	yes	no	yes	no
	4	12	2	16	4	12	10	40
	118	56	111	64	119	59	348	179
	3%	21%	2%	25%	3%	20%	3%	22%
<b>Bronchodilators/ Anti-Asthma meds</b>	yes	no	yes	no	yes	no	yes	no
	18	25	18	38	25	35	61	98
	118	56	111	64	119	59	348	179
	15%	45%	16%	59%	21%	59%	18%	55%
<b>Concomitant Oxygen Therapy</b>	yes	no	yes	no	yes	no	yes	no
	3	6	1	8	2	7	6	21
	118	56	111	64	119	59	348	179
	3%	11%	<1%	13%	2%	12%	2%	12%

\* The rest were mainly white

\*\*Isolated at Pre-treatment

**MO COMMENT:** As can be seen, significant differences were seen between smokers and nonsmokers in regards to age (smokers were younger), race (more smokers were Black), concomitant medication usage (smokers used less inhaled or systemic corticosteroids, less bronchodilators or anti-asthmatic medications), and concomitant oxygen usage (smokers used less).

The overall message from all this is that because the inclusion criteria did not use any objective measure of separating out patients with underlying pulmonary disease (i.e. more elderly patients with true chronic obstructive pulmonary disease), young patients, some as young as 18 years of age, with chronic chemical bronchitis due to smoking were included in large numbers into the protocol. Given the distribution of the data as shown above, it makes sense that smokers did better than non-smokers because the smokers were younger and less co-morbid

#### Clinical Cure Rates by Pathogen

The cure rates for Clinically Evaluable patients with at least one pre-treatment sputum pathogen were 89% in the 5-day gatifloxacin arm, 85% in the 7-day gatifloxacin arm, and 91% in the clarithromycin arm (95% CI for the difference in cure rates between 5-day gatifloxacin and clarithromycin arms: -9.3%, 6.6%). Clinical cure rates were generally comparable for the three treatment arms for the 5 major pathogens for this application, namely *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, and *S. aureus*. Out of 45 patients with *S. pneumoniae* isolates, 3 patients were considered to have a failed response due to persistence or worsening of primary signs or symptoms at least one day after completion of therapy. Two patients were in the 5-day gatifloxacin arm (005-025 and 051-553) and one in the 7-day gatifloxacin arm (005-030). *S. pneumoniae* was eradicated from sputum cultures obtained at the Test of Cure Visit for two patients (005-025 and 005-030) and was attributed to be presumed persistent for the third patient. All 18 patients with *S. pneumoniae* in the clarithromycin arm were considered cured.

**Table 18A: Clinical Cure Rates by Pathogen; Clinically Evaluable Patients**

Pathogen <sup>a</sup> /Subtype	Number Cured/Number Isolated (%)		
	5D Gatifloxacin N = 151	7D Gatifloxacin N = 154	Clarithromycin N = 163
Total patients with pathogens	83/93 (89)	76/89 (85)	90/99 (91)
<i>H. influenzae</i>	15/15 (100)	20/22 (91)	16/18 (89)
<i>S. pneumoniae</i>	14/16 (88)	10/11 (91)	18/18 (100)
<i>M. catarrhalis</i>	11/13 (85)	9/13 (69)	17/17 (100)
<i>H. parainfluenzae</i>	14/16 (88)	9/10 (90)	8/10 (80)
<i>S. aureus</i>	24/27 (89)	25/27 (93)	30/32 (94)

<sup>a</sup> A patient may have had more than one pathogen isolated pre-treatment.

**MO COMMENT:** Reviewer agrees with the data presented in the above table (adapted from applicant's Table 10.1.1.4). Crt Datasets "Evbaxrsp" and "Culture" were reviewed and the numbers concur with above. The confidence interval for the difference in cure rates of those patients with a pathogen was acceptable. Furthermore, cure rates were comparable for the 5 respiratory pathogens isolated most commonly. The numbers for *S. pneumoniae* in the other study (065) was 7/12 cured (58%) in the subset of clinically evaluable patients for 5-day gatifloxacin arm as compared to 7/10 cured (70%) in the comparator arm (azithromycin). These numbers are somewhat concerning. Combining with this current study (064) gives us a combined cure rate of 21/28 or 71% as compared to 25/28 or 89% for the comparator arms (clarithromycin in 064 study + azithromycin in 065 study). Although these proportions are not statistically different, cure rates for 5-day gatifloxacin are definitely lower than the comparators. We will need to look at the supportive study from Europe regarding this pathogen (to be discussed in the Integrated Summary)

Removing sites 23 and 24 from the analysis does not change the overall comparability between the three treatment arms. The numbers of patients with pathogens are decreased (36% of total patients with pathogens) by in similar proportion to the number of patients removed (36% of clinically evaluable patients).

Moreover, for each of the five pathogens in question, similar proportions of patients were left after removal of site 23 and 24 patients with the specific organisms.

**Table 19: Clinically Evaluable Patients with Pathogen-% Original Patients Left (-23/24)**

	Original Number	Without sites 23 & 24	% of original left
# of Clinically Eval Pts	N=468	N=300	64%
Pts with pathogen	N=281	N=180	64%
Total number of Clinically Evaluable Patients with specific organisms as follows:			
<i>H. influenzae</i>	N=55	N=33	60%
<i>M. catarrhalis</i>	N=43	N=32	74%
<i>S. pneumoniae</i>	N=45	N=28	62%
<i>H. parainfluenzae</i>	N=36	N=19	53%
<i>S. aureus</i>	N=86	N=48	56%

**Table 18B: Clinical Cure Rates by Pathogen; Clinically Evaluable Patients (-23/24)**

Pathogen <sup>a</sup> /Subtype	Number Cured/Number Isolated (%)		
	5D Gatifloxacin N = 97	7D Gatifloxacin N = 102	Clarithromycin N = 101
Total patients with pathogens	55/63 (89)	47/59 (80)	52/59 (88)
<i>H. influenzae</i>	12/12 (100)	12/13 (92)	8/8 (100)
<i>S. pneumoniae</i>	12/14 (86)	5/6 (56)	8/8 (100)
<i>M. catarrhalis</i>	9/11 (82)	6/10 (60)	11/11 (100)
<i>H. parainfluenzae</i>	7/7 (100)	5/6 (83)	4/6 (67)
<i>S. aureus</i>	12/14 (86)	16/17 (94)	15/7 (88)

<sup>a</sup>A patient may have had more than one pathogen isolated pre-treatment

**Microbiologically Evaluable Patients**

The clinical cure rates by pathogen for Microbiologically Evaluable patients with a pathogen was 90% for those treated with 5-day gatifloxacin, 88% for 7-day gatifloxacin and 93% for the clarithromycin treated group. The 95% confidence interval for the difference in response rates between 5-day gatifloxacin and clarithromycin just made the 15% lower limit at (-14.7%, 3.3%). The 95% confidence interval for the difference in response rates between the 5-day gatifloxacin vs. 7-day gatifloxacin was (-10.5%, 10.5%). The confidence interval exceeded the 15% lower limit for the comparison of response rates between 7-day gatifloxacin versus 10-day clarithromycin at (-17.6%, 2.0%).

The total bacteriologic eradication rates by pathogen for Microbiologically Evaluable patients was 98% in the 5-day gatifloxacin arm, 94% for the 7-day gatifloxacin arm, and 98% for clarithromycin arm. These results, as well as the outcomes by individual pathogens largely paralleled the results seen in the Clinically Evaluable population. Eradication rates for *S. pneumoniae* were 93% (14/15) for 5-day gatifloxacin arm, 100% (10/10) for 7-day gatifloxacin arm, and 100% (16/16) for clarithromycin arm (Table below)

**Table 20A: Eradication Rates by Pathogen; Microbiologically Evaluable Patients (+23/24)**

Pathogen	Number Eradicated/No. Isolated (%)		
	5D Gatifloxacin N = 70	7D Gatifloxacin N = 65	Clarithromycin N = 76
Total	85/87 (98)	75/80 (94)	87/89 (98)
<i>H. influenzae</i>	15/15 (100)	21/22 (95)	18/18 (100)
<i>S. pneumoniae</i>	14/15 (93)	10/10 (100)	16/16 (100)
<i>M. catarrhalis</i>	13/13 (100)	11/13 (85)	17/17 (100)
<i>H. parainfluenzae</i>	13/13 (100)	9/10 (90)	6/8 (75)
<i>S. aureus</i>	21/22 (95)	22/23 (96)	23/23 (100)

**MO COMMENT:** *There were adequate numbers of patients harboring H. influenzae, M. catarrhalis, S. pneumoniae, H. parainfluenzae or S. aureus for assessment of efficacy. There were insufficient data to show effectiveness against penicillin-intermediate and penicillin-resistant S. pneumoniae. Since in so many cases the pathogen eradication rates was presumed, a summary of the dataset "EVBRSP" was done by this reviewer to assure that comparable numbers of patients were designated as Presumed Eradicated for the different arms.*

**Table 21: Comparison of the Three Arms of Study – Eradication Assignment**

Drug	Eradicated	Persisted	Presumed Persisted	Presumed Eradicated
5D Gatifloxacin	12	1	5	123
7D Gatifloxacin	12	4	14	105
Clarithromycin	15	5	3	120

*Removing sites 23 and 24 does not change the comparability of the three arms. The bacteriologic eradication rates of the microbiologically evaluable patients for the 5 pathogens remain high across the board. However, the numbers become quite small. The total number of isolates (all three arms together) for H. influenzae is 33 (down 40%), for S. pneumoniae is 21 (down 49%), for M. catarrhalis is 32 (down 26%), for H. parainfluenzae is 15 (down 52%), and for S. aureus is 38 (down 46%).*

**Table 20B: Bacteriologic Eradication Rates by Pathogen - ME Patients (-23/24)**

Pathogen	Number Eradicated/No. Isolated (%)		
	5D Gatifloxacin N = 43	7D Gatifloxacin N = 43	Clarithromycin N = 41
Total	49/51 (96)	44/49 (90)	40/42 (95)
<i>H. influenzae</i>	12/12 (100)	12/13 (92)	8/8 (100)
<i>S. pneumoniae</i>	12/13 (93)	5/5 (100)	6/6 (100)
<i>M. catarrhalis</i>	11/11 (100)	8/10 (80)	11/11 (100)
<i>H. parainfluenzae</i>	5/5 (100)	5/6 (83)	2/4 (50)
<i>S. aureus</i>	9/10 (90)	14/15 (93)	13/13 (100)

The trends in bacteriologic eradication rates for relevant pathogens were similar to those reported for Microbiologically Evaluable Patients. The overall eradication rates in the Eligible population were 92% for 5-day gatifloxacin, 87% for 7-day gatifloxacin, and 92% for clarithromycin treatment arms. There were 10 documented persistent pathogens in the Eligible population, one in the 5-day gatifloxacin arm, four in the 7-day gatifloxacin arm, and five in the clarithromycin arm. The persistent isolate in the 5-day gatifloxacin arm was *P.aeruginosa* and the patient was assessed as a failure. In the 7-day gatifloxacin group, two patients were assessed as cured (with the persistent pathogens *P.aeruginosa* and *S. maltophilia*) and two patients were assessed as failed (with the persistent pathogens *P. aeruginosa* and *E.coli*). In the clarithromycin arm, one patient was assessed as a cure (with pathogen *S. marcescens*) and three patients were assessed as failures (with pathogens *P.mirabilis*, *K.pneumoniae*, *S.aureus*, and *P.aeruginosa*).

**Table 22: Bacteriologic Eradication Rates; Clinically Eligible Patients (+23/24, Applicant's Analysis)**

Pathogen Response	Number of Patients (%)		
	5D Gati (N=170)	7D Gati (N=171)	Clarithro (N=174)
Eradicated	134 (92)	116 (87)	135 (92)
Failure	12 (8)	18 (13)	11 (8)

**Clinical Failures**

Fifty-two patients had a clinical response of Failure with persistence and/or worsening of primary signs and symptoms as the most frequent reason for being judged a treatment failure.

**Table 23: Reason Clinical Response is Failure; Clinically Evaluable Patients (+23/24)**

Reason	Number of Patients:				
	5D Gati N=151	7D Gati N=154	Clarithro N=163	Total N=468	
Persistence/worsening of primary S & S	12	18	14	45	
Other antibiotics given despite improvement	3	--	4	6	
Clinical/x-ray evidence of pneumonia	1	--	--	1	
<b>Total = 56:</b>	<b>16</b>	<b>18</b>	<b>18</b>	<b>52</b>	

One patient in each of the three treatment groups was a treatment failure during study drug administration. The rest of the failures occurred after completion of therapy. Overall the two most frequent symptoms that related to failures were cough and increased sputum production.

Among the Clinically Evaluable Patients, there were four discrepancies between the Investigator's assignment of clinical response and those of the BMS blinded reviewer. All four were assigned as CURED by the investigator but FAILED by the BMS monitor. One patient was in the 5-day gatifloxacin arm and the rest in the 7-day gatifloxacin arm. Among All Treated Patients, there were 42 Discrepancies (14 in the 5-day gatifloxacin arm, 19 in the 7-day gatifloxacin arm, and 9 in the clarithromycin arm. Discrepancies were most often due to differences in the definition for the Unable to Determine response. protocol. The applicant's appendix 4, which presented all the discrepancies, was reviewed to assure that similar numbers of reassignment occurred in both treatment arms.

**Table 23: Comparison of the Three Study Arms – Reassignment of Clinical Response**

Reassignment by BMS	5 D gatifloxacin (14 discrepancies)	7 D gatifloxacin (19 discrepancies)	Clarithromycin (9 discrepancies)
UTD to Cured	11	12	8
UTD to Failure	3	4	1
Cured to Failure	--	3	--

**MO COMMENT:** The reasons for clinical failure across the three arms of study were similar. Likewise, comparable numbers of patients were similarly reassigned across the three arms.