

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**21-061 and 21-062**

**STATISTICAL REVIEW(S)**

ATEMS  
Barrato

# STATISTICAL REVIEW AND EVALUATION

NOV 2 1999

**NDA#:** 21-061 and 21-062

**Name of Drug:** TEQUIN™ Tablets (gatifloxacin) and  
TEQUIN™ I.V. (gatifloxacin)

**Applicant:** Bristol-Myers Squibb Company

**Indications:** 7 total, the following 3 by this reviewer:  
(1) community-acquired pneumonia,  
(2) acute exacerbation of chronic bronchitis,  
(3) acute sinusitis,  
The statistical review of complicated and uncomplicated urinary tract infections and skin and skin structure infections was completed by Nancy Silliman, Ph.D.. No statistical review was required for uncomplicated gonococcal urethritis/cervicitis.

**Documents Reviewed:** Volumes 1.165 – 1.178, 1.189 – 1.193 and electronic submission dated December 28, 1998, and major multi-discipline amendment number 15 dated June 11, 1999.

**Review Type:** Clinical data

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**Keywords:** quinolone, fluoroquinolone, dynamic randomization

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## I. INTRODUCTION

Tequin™ (gatifloxacin) is a new fluoroquinolone antibiotic developed by Kyorin Pharmaceutical Co. Ltd. (Tokyo, Japan). The clinical program was sponsored by Bristol-Myers Squibb (BMS) and was submitted as an NDA on December 28, 1998. The clinical program focused on seven indications. The respiratory indications consisted of community-acquired pneumonia, acute exacerbation of chronic bronchitis and acute sinusitis. The remaining indications were complicated and uncomplicated urinary tract infections, skin and skin structure infections and uncomplicated gonococcal urethritis/cervicitis. Gatifloxacin was administered 400 mg per day, with additional doses (200mg and 600 mg for the uncomplicated urinary tract infections and gonorrhea indications, respectively). Both an oral and parenteral formulation were studied. There were a total of 12 phase III and 4 open-label phase II studies. The majority of the clinical program was conducted in the US and Canada. Four studies included sites in other countries including Argentina, Australia, Brazil, Mexico, Puerto Rico, and South Africa. This review will focus on the 7 controlled clinical studies conducted in support of the three respiratory indications.

The community-acquired pneumonia indication was studied in 3 phase III comparative studies (AI420-002, AI420-037, and AI420-038) and 2 phase II non-comparative studies (AI420-003 and AI420-006). Gatifloxacin was administered orally in AI420-002 and IV to oral in -037 and -038. These two studies will serve as the basis for the approval of the IV formulation. The comparator treatments were clarithromycin, ceftriaxone with or without erythromycin, and levofloxacin. The acute exacerbation of chronic bronchitis indication was studied in 2 phase III comparative studies (AI420-001 and AI420-020) and one phase II non-comparative study (AI420-004). The comparators were levofloxacin and cefuroxime axetil. The acute sinusitis indication was studied in 2 phase III comparative studies (AI420-008 and AI420-066) and one phase II non-comparative study (AI420-007). Study AI420-066 was submitted in as a major amendment to the NDA in June of 1999. The comparators were clarithromycin and trovafloxacin.

Bristol-Myers Squibb conducted all of their randomized controlled studies submitted in the NDA except study AI420-066 using a dynamic randomization algorithm to balance treatment assignment within site and across additional stratification factors. The algorithm used was the Pocock minimization algorithm (Pocock SJ and Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-115). This algorithm will assign drugs with equal probability (50%) only if there is no imbalance in sample size between the two treatments. If there is an imbalance, the drug with fewer assignments will have a greater change of being assigned. The probability of being assigned increases as the imbalance increases. The following table states the probability of assignment by the extent of imbalance. Note that in countries other than the US or Canada, randomization took place using drug assignment logs.

<u>Maximum Potential Imbalance</u>	<u>Probability of assigning treatment with least imbalance</u>
7 or more	90%
5 or 6	75%
1 to 4	67%
0	50%

The reason this method is used is that it assures almost equal numbers of subjects on the two treatment arms within each site and within each level of additional stratification variables (i.e., smoking status). However, the use of this method complicates the interpretation of the results. At the present time we do not know of any appropriate analysis that takes this randomization into account. The analyses shown in this report assume that a simple randomization technique was used. It is not known if the results reported in this review are more or less conservative due to the dynamic randomization. At the request of the FDA, BMS conducted simulations to attempt to address this issue. Though only a fixed number of possible scenarios could be simulated, the results showed that results based on data randomized using the Pocock-Simon randomization technique were not less conservative than results based on data randomized using simple randomization or permuted block randomization. Since the conclusions could not be proven theoretically, the true affect of dynamic randomization on the results is unknown. However, based on these simulations we feel that the results in this application can be expected to be similar to the results that would have been obtained had simple randomization been used.

The following table gives the sponsor's study results for the three indications discussed in this review. Using a limit for equivalence of -15%, all of the studies except one acute sinusitis meet this limit. Sections II, III, and IV of this review will cover each of these three respiratory indications separately.

<i>Summary of Sponsor's results for the three respiratory indications, all treated patients (AT) and the evaluable patients (Eval) data sets</i>				
<i>Cure Rate</i>				
		<i>Gatifloxacin</i>	<i>Comparator</i>	<i>95% C.I.*</i>
<i>Community-Acquired Pneumonia</i>				
Study AI420-002	AT	82%	86%	(-12.8, 3.2)
	Eval	88%	91%	(-10.1, 5.1)
Study AI420-037	AT	73%	70%	(-8.4, 14.8)
	Eval	88%	85%	(-7.6, 15.3)
Study AI420-038	AT	83%	88%	(-13.1, 2.8)
	Eval	90%	93%	(-11.5, 3.6)
<i>Acute Exacerbation of Chronic Bronchitis</i>				
Study AI420-001	AT	78%	84%	(-14.9, 3.4)
	Eval	88%	92%	(-14.6, 6.2)
Study AI420-020	AT	80%	78%	(-6.3, 10.7)
	Eval	86%	83%	(-4.8, 11.4)
<i>Acute Sinusitis</i>				
Study AI420-008	AT	62%	63%	(-10.0, 9.6)
	Eval	72%	76%	(-15.2, 6.7)
Study AI420-066	AT	81%	76%	(-6.6, 16.7)
	Eval	88%	87%	(-9.6, 12.2)

\*95% Confidence interval for the difference in cure rates.

## II. COMMUNITY-ACQUIRED PNEUMONIA

Three phase III and 2 phase II/III studies were conducted for the indication of community-acquired pneumonia; 3 active-controlled blinded studies (AI420-002, AI420-037, and AI420-038) and two open-label non-comparative studies (AI420-003 and AI420-006). A total of 1326 patients were studied; 1131 in the controlled studies and 195 in the open-label studies. Study AI420-003 and -006 were designed to establish the clinical and bacteriologic efficacy of gatifloxacin in the treatment of acute community-acquired bacterial pneumonia and to establish the clinical efficacy in the treatment of atypical pneumonia. Study AI420-002 and -038 were designed to demonstrate the safety and efficacy of gatifloxacin compared to clarithromycin and levofloxacin, respectively, in adults with community-acquired pneumonia. Study AI420-037 was designed to demonstrate the safety and efficacy of gatifloxacin compared to ceftriaxone with or without erythromycin in adults with community-acquired pneumonia requiring hospitalization. The studies had very similar designs and conduct. Only the controlled studies will be discussed in this review. For a complete discussion of Studies AI420-003 and AI420-006 please see the medical officer's review.

**Protocol AI420-002: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, COMPARATIVE PHASE III STUDY OF GATIFLOXACIN VERSUS CLARITHROMYCIN IN THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA**

**Protocol AI420-037: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, COMPARATIVE PHASE III STUDY OF GATIFLOXACIN VERSUS CEFTRIAXONE IN THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA REQUIRING HOSPITALIZATION**

**Protocol AI420-038: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, COMPARATIVE PHASE III STUDY OF GATIFLOXACIN VERSUS LEVOFLOXACIN IN THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA**

### **1. Objectives and Study Design**

These studies were randomized (1:1), double-blind, multi-center, two arm comparative studies. Four hundred thirty two non-hospitalized patients were enrolled in AI420-002, 287 newly hospitalized patients were enrolled in AI420-037 and 418 newly hospitalized or non-hospitalized patients were enrolled in AI420-038. The objective of studies AI420-002, -037, and -038 was to establish clinical efficacy and safety of gatifloxacin compared to standard regimens of clarithromycin, ceftriaxone with or without erythromycin, and levofloxacin in the treatment of community-acquired pneumonia. Study AI420-002 was conducted at 87 study sites (59 enrolled patients) in the US, Canada, Mexico, South Africa, Puerto Rico, Brazil, Australia, and Argentina from June 23, 1997 to June 24, 1998. Study AI420-037 was conducted at 61 study sites (45 enrolled patients) in the US and Canada from November 16, 1997 to June 26, 1998. Study AI420-038 was conducted at 61 study sites (48 enrolled patients) in the US from November 6, 1997 to June 11, 1998.

*Reviewer's comment: The studies used a dynamic randomization algorithm to assign subjects to treatments while ensuring balance between the two treatments within center and, in study AI420-038, by initial route of administration (IV/PO) (Pocock SJ and Simon R. Sequential treatment*

assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-115). At the present time we do not know of any appropriate analysis that takes this randomization into account. The analyses shown in this report assume that a simple randomization technique was used. It is not known if the results reported in this review are more or less conservative due to the dynamic randomization. Additional details of this issue are given in the Introduction. Note that for sites located outside the US and Canada treatment assignment was achieved by using drug assignment logs. Each log page assigned an equal number of gatifloxacin and comparator treatments in random order.

Gatifloxacin was administered for 7 – 14 days as

- 400 mg PO in study AI420-002,
- 400 mg IV daily +/- step-down to gatifloxacin 400 mg PO daily in study AI420-037,
- 400 mg PO only, IV only, or IV to PO in study AI420-038.

The active control was administered for 7 – 14 days as

- 500 mg PO twice daily of clarithromycin in study AI420-002,
- 1 or 2 gm IV daily of ceftriaxone with or without erythromycin 0.5 or 1 gm IV every 6 hours (+/- step-down to clarithromycin 500 mg PO twice daily) in study AI420-037,
- 500 mg PO only, IV only, or IV to PO daily of levofloxacin in study AI420-038.

Note that in study AI420-037 at the investigator's discretion, the patients could be converted to oral gatifloxacin or clarithromycin (with or without erythromycin) at any time after 2 days of IV therapy. In study AI420-038 it was at the investigator's discretion whether patients received oral therapy, IV therapy, or IV followed by oral therapy.

*Reviewer's Comment:* For clarification on treatments for study AI420-037: The investigator would order a dose of ceftriaxone (1 gm or 2 gm QD) for each patient and, if atypical pneumonia was suspected, a dose of erythromycin (500 mg or 1 gm every 6 hours). The pharmacist who was unblinded to the randomization would then dispense the appropriate IV study drug, either gatifloxacin 400 mg IV QD +/- placebo erythromycin IV every 6 hours or ceftriaxone-1 or 2 gm IV QD +/- erythromycin 500 or 1000 mg IV every 6 hours. There are 6 possible comparator regimens for study AI420-037: ceftriaxone 1 gm, ceftriaxone 2 gm, ceftriaxone 1 gm + erythromycin 500 mg, ceftriaxone 2 gm + erythromycin 500 mg, ceftriaxone 1 gm + erythromycin 1 gm, and ceftriaxone 2 gm + erythromycin 1 gm.

The primary inclusion criteria were a new infiltrate on chest x-ray, and two or more of the following:

- fever (>38°C);
- leukocytosis;
- cough;
- purulent sputum (>25 PMN and <10 squamous epithelial cells per low power field);
- chest pain;
- auscultatory findings such as rales or egophony.

Study AI420-002 also included “- chills”, “- headache” and “- malaise”. Studies AI420-037 and -038 also included “- transtracheal aspirate, bronchial brushings, or biopsy material that reveals neutrophils and a predominant pathogen suspected by smear” and “- direct lung aspirate with identification of a predominant pathogen.” Subjects in study AI420-037 had to be newly hospitalized (<24 hours). Patients who were determined to be ineligible for the study after they

were enrolled and treated with the study medication were included in the intent-to-treat analyses and removed from the per-protocol analyses.

The following notation is used to indicate study periods: first day of study drug therapy is Day 1, days on which study drug was administered are Day 1, Day 2, Day 3, etc., pre-treatment days are Day -2, Day -1, etc., and post-treatment days are Day +1, Day +2, etc.. Patients were evaluated pre-treatment, during treatment, end of treatment, post-treatment (Day +7 to Day +14), and final follow-up (Day +21 to Day +28). The clinical response was based on the signs and symptoms reported at the Test of Cure visit conducted between Day +5 to Day +28, or earlier for those who discontinued. This Test of Cure visit window was extended from the original Day +7 to +14. This change was made in the Analysis Plan submitted on June 19, 1998; study unblinding was done on October 1, 1998 for AI420-002, on October 5, 1998 for AI420-037 and on September 21, 1998 for AI420-038. Relapse was assessed at the final follow-up between Day +21 and Day +28.

*Reviewer's Comment: The revised Test of Cure visit window of +5 to +28 contains the final follow-up window of +21 to +28. This issue is discussed in section 4.*

At the Test of Cure visit a clinical response of cured, failure, or unable to determine (UTD) was recorded for each subject. Treatment failures could be assessed anytime after 3 days of treatment. The primary efficacy variable as defined by the sponsor was the clinical response rate at the Test of Cure visit in clinically evaluable patients. The FDA considers analyses based on the intent to treat population as co-primary. The definitions of cure, failure, and unable to determine given on page 48 of the BMS study report for AI420-002 are shown here:

#### CURED

- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and chest x-ray abnormalities were improved or had not progressed, OR
- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and no during or post-treatment chest x-ray was performed (These patients were not included in the evaluable subset).

#### FAILURE

One or more of the following:

- Signs and symptoms relevant to the original infection persisted or progressed after at least 3 days of study therapy,
- New pulmonary or extrapulmonary clinical findings consistent with pneumonia developed,
- Radiographic abnormalities progressed,
- Additional antimicrobial therapy was needed for treatment of the pneumonia under study,
- Patient died and death was due to pneumonia.

#### UNABLE TO DETERMINE

Extenuating circumstances which precluded classification as Cure or Failure; for example:

- A Test of Cure evaluation of clinical signs and symptoms was not obtained, or
- Another systemic antibiotic with documented (i.e., according to the package insert) activity against the causative pathogen was administered for an infection other than pneumonia between the pre-treatment and Test of Cure Visits.

*Reviewer's Comment: Amendments to the protocol were made for study AI420-002 on 10/20/97 and 10/30/97 that changed the definition of cured from "All acute signs of pneumonia have resolved and chest x-ray abnormalities have either improved or not progressed."*

Subjects were tested for pre-treatment pathogens from sputum and/or blood culture (an atypical pathogen was diagnosed by culture, PCR, and/or serology). Each pre-treatment pathogen was then assigned a bacteriologic response at the end of study based on either a post-treatment culture or the subject's clinical response. The bacteriologic responses were: Eradicated based on a post-treatment culture, Presumed Eradicated if there was not a post-treatment culture and the subject was clinically cured, Persisted based on a post-treatment culture, and Presumed Persisted if there was not a post-treatment culture and the subject was a clinical failure.

Four data sets were of interest in the analyses. The exact definitions of the data sets from page 56 of the study report for AI420-002 are given here:

- All Treated Patients: All patients known or suspected to have received at least one dose of either study drug.
- Clinically Eligible Patients: All Treated Patients with a diagnosis of community-acquired pneumonia at entry, defined as:
  - a new infiltrate(s) on chest x-ray, and
  - two or more of the following:
    - fever (>38°C for 100.4°F)
    - leukocytosis (>10,000 WBC/mm<sup>3</sup> or >15% bands)
    - cough
    - purulent sputum (>25 PMN and <10 squamous epithelial cells per low power field) with or without identification of a predominant suspected pathogen by microscopy
    - chest pain
    - auscultatory findings such as rales or egophony
    - chills headache
    - malaise
- Clinically Evaluable Patients: All Clinically Eligible Patients who:
  - Received at least 5 days of treatment with study drug (at least 3 days for patients classified as treatment failures),
  - Received a Test of Cure assessment in the interval Day +5 to Day +28, or earlier in the case of failure, and
  - Did not receive a systemic antibacterial agent with documented (i.e., in the package insert) activity against the causative pathogen, or is predictably active against respiratory pathogens (if no pathogen was isolated for the patient), between the start of study therapy and the Test of Cure Visit,
- Microbiologically Evaluable Patients: All Clinically Evaluable Patients who:
  - Had at least one bacterial pathogen susceptible to both study drugs isolated from pre-treatment sputum and/or blood culture, or an atypical pathogen diagnosed by culture, PCR, and/or serology,
  - Had a post-treatment sputum Gram stain performed, if the patient was still producing sputum,
  - Had a post-treatment sputum culture performed, if the patient was still producing sputum and the sample was of good quality (i.e., >25 PMN/LPF and <10 epithelial cell/LPF).

Included in the criteria for "Eligible Patients" for AI420-037 and -038 were " - transtracheal aspirate, bronchial brushings, or biopsy material with Gram stain which reveals neutrophils, and a predominant pathogen suspected by smear" and " - direct lung aspirate with identification of a

predominant pathogen on Gram stain." Not included in the criteria for "Eligible Patients" for AI420-037 were " - chills headache" and " - malaise".

## 2. Study Population and Baseline Demographics

### *Study AI420-002*

A total of 432 patients were enrolled in 59 study centers. Of the subjects enrolled in the study, 431 patients were treated; 217 received gatifloxacin and 214 received levofloxacin. One subject on gatifloxacin was labeled as not taking any study medication and was removed from all of the data sets. Four hundred thirteen patients (96% of all treated patients) were considered in the Eligible data set. Three hundred eighty one patients (88% of all treated patients) were considered Clinically Evaluable (191 on gatifloxacin and 190 on clarithromycin). One hundred eighty four patients were microbiologically evaluable. Table II.1 below contains the specific information on the protocol violations/reasons for exclusions (from Table 8.1B BMS study report for AI420-002).

### *Study AI420-037*

A total of 287 patients were enrolled in 45 study centers. Of the 287 subjects enrolled in the study, 3 patients were not treated with study medication (1 randomized to gatifloxacin and 2 randomized to ceftriaxone). One subject who was randomized to ceftriaxone erroneously received oral gatifloxacin as step-down therapy. These 4 subjects were removed from the analysis. The all treated data set contains 283 patients, 141 patients on the gatifloxacin arm and 142 on the ceftriaxone arm. Two hundred seventy six patients (98% of all treated patients) were considered in the Eligible data set. Two hundred twelve patients (75% of all treated patients) were considered Clinically Evaluable (104 on gatifloxacin and 108 on ceftriaxone). One hundred four patients were microbiologically evaluable. Table II.1 below contains the specific information on the protocol violations/reasons for exclusions (from Table 8.1B BMS study report for AI420-037).

### *Study AI420-038*

A total of 418 patients were enrolled in 48 study centers. Of the subjects enrolled in the study, 417 patients were treated; 209 received gatifloxacin and 208 received levofloxacin. One subject randomized to levofloxacin was not treated and was removed from all of the data sets. Four hundred patients (97% of all treated patients) were considered in the Eligible data set. Three hundred fifty patients (84% of all treated patients) were considered Clinically Evaluable (172 on gatifloxacin and 178 on levofloxacin). One hundred seventy three patients were microbiologically evaluable. Table II.1 below contains the specific information on the protocol violations/reasons for exclusions (from Table 8.1B BMS study report for AI420-038).

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Table II.1

**Distribution of Patients in Study Populations and  
Reasons for Exclusion, All Treated Patients  
Protocol AI420-002, AI420-037 and AI420-038**

Reason	Study AI420-002		Study AI420-037		Study AI420-038	
	Number of Patients (%)		Number of Patients (%)		Number of Patients (%)	
	Gatifloxacin	Clarithro.	Gatifloxacin	Ceftriaxone	Gatifloxacin	Levo.
<b>Treated</b>	<b>217</b>	<b>214</b>	<b>141</b>	<b>142</b>	<b>209</b>	<b>208</b>
<b>Eligible</b>	<b>207 (95)</b>	<b>205 (96)</b>	<b>136 (96)</b>	<b>140 (99)</b>	<b>203 (97)</b>	<b>197 (95)</b>
<b>Ineligible</b>	<b>10 (5)</b>	<b>9 (4)</b>	<b>5 (4)</b>	<b>2 (1)</b>	<b>6 (3)</b>	<b>11 (5)</b>
<u>Reason Ineligible:</u>						
No evidence of pneumonia on pre-treatment x-ray	9 (4)	9 (4)	5 (4)	2 (1)	5 (2)	11 (5)
No study medication given	1* (<1)	-	-	-	-	-
Received > 1 dose of pre-treatment antibiotic	-	-	-	-	1 (<1)	-
<b>Clinically Evaluable</b>	<b>191 (88)</b>	<b>190 (89)</b>	<b>104 (74)</b>	<b>108 (76)</b>	<b>172 (82)</b>	<b>178 (86)</b>
<b>Clinically Unevaluable</b>	<b>26 (12)</b>	<b>24 (11)</b>	<b>37 (26)</b>	<b>34 (24)</b>	<b>37 (18)</b>	<b>30 (14)</b>
<u>Reason Unevaluable:</u>						
No Test of Cure visit	2 (1)	4 (2)	7 (5)	6 (4)	14 (7)	8 (4)
Patient Clinically Ineligible	10 (5)	9 (4)	5 (4)	2 (1)	6 (3)	11 (5)
Inadequate dosing	9 (4)	6 (3)	14 (10)	18 (13)	11 (5)	6 (3)
Concomitant systemic antibiotic given	1 (<1)	1 (<1)	5 (4)	5 (4)	1 (<1)	2 (1)
>1 dose of pre-treatment systemic antibiotic	1 (<1)	1 (<1)	2 (1)	3 (2)	1 (<1)	-
Test of Cure visit outside "window"	2 (1)	3 (1)	4 (3)	-	2 (1)	2 (1)
Other	1 (<1)	-	-	-	2 (1)	1 (<1)
<b>Microbiologically Evaluable</b>	<b>90 (41)</b>	<b>94 (44)</b>	<b>50 (35)</b>	<b>54 (38)</b>	<b>92 (44)</b>	<b>81 (39)</b>
<b>Microbiologically Unevaluable</b>	<b>127 (59)</b>	<b>120 (56)</b>	<b>91 (65)</b>	<b>88 (62)</b>	<b>117 (56)</b>	<b>127 (61)</b>
<u>Reason Unevaluable:</u>						
Clinically Unevaluable	5 (2)	11 (5)	14 (10)	15 (11)	15 (7)	10 (5)
No pathogen documented	111 (51)	102 (48)	70 (50)	65 (46)	102 (49)	116 (56)
Pathogen resistant to study drug(s)	11 (5)	7 (3)	7 (5)	8 (6)	-	1 (<1)

\*One patient inappropriately classified as ineligible

*Reviewer's Comments:* One subject in study AI420-002 was known to have received a single dose of gatifloxacin but was lost to follow-up. This patient was labeled as ineligible with no study medication received although he should have been labeled as eligible but unevaluable. The outcome for this subject was unable to determine. We used the locked database in our analyses, since changing this subject to eligible would not have changed the results of the analyses. The subject listed as "other" for clinically unevaluable was unevaluable because the subject withdrew from the study on day 7 due to AE's and placed on alternative antibiotics.

In study AI420-037, subjects assigned to low dose of ceftriaxone had a lower evaluability rate than those assigned to the high dose. The evaluability rate for the low dose was 69% (68% gatifloxacin and 69% ceftriaxone). The evaluability rate for high dose was 89% (86% on gatifloxacin and 91% on ceftriaxone). The low dose had a higher proportion of unevaluable for many of the categories including "inadequate dosage", "no test of cure visit" and "patient ineligible".

*In study AI420-038, one subject who was considered microbiologically evaluable was not clinically evaluable. This subject should be removed from the analysis of the microbiologically evaluable data. The number of microbiologically evaluable subjects for gatifloxacin should be 91. This subject will be relabeled as not microbiologically evaluable for our analyses.*

There were not large differences in the demographic characteristics gender, race, age and weight between the two treatment groups in the studies. In study AI420-002, 46% of the gatifloxacin arm and 54% clarithromycin were female. In study AI420-037, 56% of the gatifloxacin arm and 46% of the ceftriaxone arm were female. In this study there was a higher proportion of black patients in the ceftriaxone arm (21% vs. 12% in gatifloxacin). In study AI420-038, 51% of the gatifloxacin arm and 59% of the levofloxacin arm were female. There were not large differences in recorded pulmonary history, medical history, use of pre-treatment antimicrobial medications, prognostic factors, or pre-treatment signs and symptoms within any of the studies. The table below contains general demographic information pooled across treatments for the three studies.

Study	% Female	% White	% Black	% Hispanic	Age in years Mean (Range)	Weight in kg Mean (Range)
AI420-002	50	84	4	10	50 (18 - 97)	75 (33 - 155)
AI420-037	51	77	17	7	62 (18 - 92)	74 (32 - 181)
AI420-038	55	84	11	4	53 (19 - 91)	80 (36 - 203)

There were large differences in prognostic factors between study AI420-037 which enrolled only hospitalized subjects and studies AI420-002 and -038. Subjects in study AI420-037 were on average older than subjects in -002 and -038. A larger percentage of subjects in study AI420-037 had a history of comorbid disease than the other two studies (55% vs. 26% and 33%). A larger percentage of subjects in study AI420-037 had severe pneumonia than in the other two studies (73% vs. 22% and 24%).

### 3. Applicant's Analyses and Results

It was stated in the study reports that gatifloxacin would be considered effective relative to clarithromycin, ceftriaxone, or levofloxacin if the 95% confidence intervals around the differences in cure rates did not extend beyond  $\delta\%$  in favor of the comparator, where  $\delta$  equals 20 if the largest observed cure rate is less than 80%, 15 if the cure rate is between 80 and 89%, and 10 if the cure rate is 90% or larger. The confidence intervals were constructed using an exact method in StatXact-3®.

*Reviewer's comment: Based on the rule stated above, the limit for equivalence would be 10% for study AI420-002, 15% for study AI420-037, and 10% for study AI420-038. However, in line with the recent July 1998 Anti-Infective Advisory Committee meeting, we will consider the limit of equivalence to be independent of observed response. Since 15% was discussed and agreed upon by the FDA in reference to all recently submitted gatifloxacin protocols, we will use 15% in determining equivalence in this study.*

#### Study AI420-002

Table II.2 reports the results from study AI420-002 for clinical response for the all treated (AT), eligible (Elig), evaluable (Eval), and microbiologically evaluable (M. Eval) data sets. The cure rates for clarithromycin were slightly higher than for gatifloxacin in all data sets except the microbiologically evaluable data set. The confidence intervals for all four data sets are within the 15% limit.

**Table II.2 BMS study results AI420-002**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Clarithromycin			
	AT n = 217	Elig n = 207	Eval n = 191	M. Eval n = 90	AT n = 214	Elig n = 205	Eval n = 190	M. Eval n = 94
Cured	178 (82)	173 (84)	169 (88)	86 (96)	185 (86)	178 (87)	172 (91)	84 (89)
Failure	23 (11)	22 (11)	22 (12)	4 (4)	18 (8)	18 (9)	18 (9)	10 (11)
Unable to Determine	16 (7)	12 (6)	N/A	N/A	11 (5)	9 (4)	N/A	N/A
95% Confidence interval for the difference in Cure rate:					AT (-12.8, 3.2)			
					Elig (-11.7, 4.4)			
					Eval (-10.1, 5.1)			
					M. Eval (-3.8, 17.7)			

*Reviewer's comments: Study AI410-002 had sites in both North America (US and Canada) and outside North America. The cure rate was slightly higher outside North America (94%) versus North America (89%). The clarithromycin treated group had slightly higher cure rates than gatifloxacin in both geographic areas.*

*Study: AI420-037*

Table II.3 reports the results from study AI420-037 for clinical response for the all treated (AT), eligible (Elig), evaluable (Eval), and microbiologically evaluable (M. Eval) data sets. The cure rates for gatifloxacin were slightly higher than for ceftriaxone in all data sets except the microbiologically evaluable data set. The confidence intervals for all treated patients, clinically eligible and clinically evaluable patients are well within the 15% limit. The confidence interval for the microbiologically evaluable patients falls outside of the 15% limit.

**Table II.3 BMS study results AI420-037**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Ceftriaxone			
	AT n = 141	Elig n = 136	Eval n = 104	M. Eval n = 50	AT n = 142	Elig n = 140	Eval n = 108	M. Eval n = 54
Cured	103 (73)	100 (74)	92 (88)	42 (84)	100 (70)	99 (71)	92 (85)	47 (87)
Failure	13 (9)	12 (9)	12 (12)	8 (16)	19 (13)	19 (14)	16 (15)	7 (13)
Unable to Determine	25 (18)	24 (18)	N/A	N/A	23 (16)	22 (16)	N/A	N/A
95% Confidence interval for the difference in Cure rate:					AT (-8.4, 14.8)			
					Elig (-8.5, 15.0)			
					Eval (-7.6, 15.3)			
					M. Eval (-21.8, 14.0)			

*Reviewer's comments: As mentioned above, there are 6 possible comparator regimens. All subjects were assigned to a regimen based on their severity of disease and type of pneumonia (i.e., typical or atypical pneumonia). However, subjects randomized to gatifloxacin all received the same dose regardless of their assignment to a dosing regimen. The largest percentage of patients was assigned to the low dose of ceftriaxone and no erythromycin (41%). Twenty-one percent of subjects were assigned to the high dose of ceftriaxone and no erythromycin. Twenty-*

four percent of patients were assigned to the low dose of ceftriaxone and the low dose of erythromycin. Less than 10% were assigned to each of the remaining dose regimens. Table II.4 contains the number of patients assigned and number cured for each dosing regimen for the all treated data set and for the evaluable data set. An analysis by assignment to dosing regimen was conducted using the Mantel-Haenszel estimate of the 95% confidence interval with a continuity correction. The confidence intervals for both data sets are well within the -15% limit.

**Table II.4 AI420-037: Cure rates based on assignment to comparator regimen**

Assignment to dosing regimen	Number Cured/Number of Patients (% Cured)			
	Gatifloxacin		Ceftriaxone	
	AT n = 141	Eval n = 104	AT n = 142	Eval n = 108
Ceftriaxone 1 gm	45/62 (73)	39/45 (87)	40/54 (74)	35/42 (83)
Ceftriaxone 2 gm	25/30 (83)	25/29 (86)	25/29 (86)	25/27 (93)
Ceftriaxone 1 gm Erythromycin 0.5 gm	20/29 (69)	16/18 (89)	21/39 (54)	19/23 (83)
Ceftriaxone 2 gm Erythromycin 0.5 gm	7/10 (70)	7/7 (100)	9/14 (64)	9/12 (75)
Ceftriaxone 1 gm Erythromycin 1 gm	5/7 (71)	4/4 (100)	3/4 (75)	2/2 (100)
Ceftriaxone 2 gm Erythromycin 1 gm	1/3 (33)	1/1 (100)	2/2 (100)	2/2 (100)
95% Confidence interval for the difference in Cure rate, adjusting for assignment to dosing regimen:			AT (-8.8, 11.9) Eval (-6.5, 12.5)	

The following table contains the cure rates by assignment of erythromycin. Note that erythromycin was assigned along with ceftriaxone because ceftriaxone does not treat atypical pneumonia. From the breakdown given in the table it looks as if for subjects thought to have needed erythromycin, gatifloxacin does better than ceftriaxone plus erythromycin and for those subjects who were thought to not need erythromycin, ceftriaxone and gatifloxacin have similar cure rates.

Assigned Erythromycin	Clinical Cure Rate	
	Gatifloxacin	Ceftriaxone
All treated patients	Yes	67%
	No	76%
Evaluable patients	Yes	93%
	No	86%

In study AI420-037, 85% of patients received IV followed by oral therapy and 15% received IV therapy only in both treatment groups. Seventy eight percent of all patients received 7 – 14 days of treatment therapy with the percentages in the two treatment groups being similar.

*Reviewer's Comment:* Note that failures are on IV longer than cures or unable to determine. Mean IV duration for cures is 3.7 days, for failures is 5.0 days, and for unable to determine is 3.0 days. Also note that patients assigned to low ceftriaxone dose are on IV for similar number of days as those assigned to high dose. The mean for the low dose is 3.8 days and the mean for high dose is 3.7 days.

The two treatment groups are on IV for similar durations. The mean duration on IV for gatifloxacin was 3.71 days and for ceftriaxone was 3.74 days based on the all treated patients population. For the evaluable population, the mean duration on IV was 3.72 days for gatifloxacin and 4.0 days for ceftriaxone.

**Study AI420-038**

Table II.5 reports the results from study AI420-038 for clinical response for the all treated (AT), eligible (Elig), evaluable (Eval), and microbiologically evaluable (M. Eval) data sets. The cure rates for levofloxacin were slightly higher than for gatifloxacin in all four data sets. The confidence intervals for the all treated, eligible and evaluable were within the 15% limit. The microbiologically evaluable confidence interval fell outside of the 15% limit.

**Table II.5 BMS study results AI420-038**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Levofloxacin			
	AT n = 209	Elig n = 203	Eval n = 172	M. Eval n = 91	AT n = 208	Elig n = 197	Eval n = 178	M. Eval n = 81
Cured	174 (83)	168 (83)	154 (90)	83 (91)	183 (88)	175 (89)	166 (93)	77 (95)
Failure	18 (9)	18 (9)	18 (10)	8 (9)	14 (7)	12 (6)	12 (7)	4 (5)
Unable to Determine	17 (8)	17 (8)	N/A	N/A	11 (5)	10 (5)	N/A	N/A

95% Confidence interval for the difference in Cure rate:

- AT (-13.1, 2.8)
- Elig (-14.5, 1.7)
- Eval (-11.5, 3.6)
- M. Eval (-15.3, 6.9)

Reviewer's comment: In the randomization, subjects were stratified by initial route of administration, either IV or PO. The majority of subjects (88%) received the study drugs orally. Only 49 subjects (12%) were given IV. The following confidence intervals were constructed using the Mantel-Haenszel method with continuity correction using initial route of administration as a stratification factor. The 95% confidence interval for the all treated patients data set is (-11.5, 2.0). The cure rate for gatifloxacin in the IV group is 71% and for levofloxacin is 88%. There is a smaller treatment difference for the oral group where the cure rate for gatifloxacin is 85% and for levofloxacin is 88%. The confidence interval for the evaluable data set is (-9.8, 2.2). The cure rate for gatifloxacin in the IV group is 84% and for levofloxacin is 91%. The cure rate for gatifloxacin in the oral group is 90% and for levofloxacin is 94%. Note that these intervals are narrower than the confidence intervals that do not take this stratification into account.

For those subjects who were assigned to IV, the mean duration of days on IV was the same for the 2 treatment groups (2.4 days). As what might be expected, the longer duration on IV, the lower the observed cure rate.

Table II.6 (from Table 10.2.1.2 of BMS AI420-002, -037, and -038 study reports) gives the reasons why clinical responses were unable to determine in the eligible patients. Note that in the analyses of the all treated patients data set and the eligible data set, subjects whose responses were unable to determine were considered failures in the analyses.

Table II.6

**Reason Clinical Response is Unable to Determine,  
Clinically Eligible Patients  
Protocols AI420-002, AI420-037 and AI420-038**

Reason	Number of Patients (%)					
	Study AI420-002		Study AI420-037		Study AI420-038	
	Gatifloxacin N = 207	Clarithro. N = 205	Gatifloxacin N = 136	Ceftriaxone N = 140	Gatifloxacin N = 203	Levo. N = 197
<b>Number of Responses Unable to Determine</b>	12 (6)	9 (4)	24 (18)	22 (16)	17 (8)	10 (5)
Adverse event	6 (3)	3 (1)	7 (5)	7 (5)	7 (3)	1 (<1)
Inadequate follow-up	2 (1)	4 (2)	5 (4)	1 (1)	6 (3)	7 (3)
Intercurrent illness	1 (<1)	1 (<1)	2 (1)	2 (1)	1 (<1)	-
Other systemic antibiotic given for infection other than pneumonia	1 (<1)	1 (<1)	4 (3)	2 (1)	1 (<1)	2 (1)
Patient request/ Withdrew consent	1 (<1)	0 (0)	3 (2)	6 (4)	1 (<1)	-
Concomitant antibiotics	-	-	1 (1)	1 (1)	-	-
Therapy ineffective	1 (<1)	0 (0)	-	-	-	-
Death	-	-	2 (1)	-	1 (<1)	-
Other	-	-	-	3 (2)	-	-

Of the two deaths in study AI420-037, 1 was thought to be due to an underlying disease, COPD. The other was thought to be from both an underlying disease and the primary infection. The subject died after receiving one dose of IV gatifloxacin of group A streptococcal sepsis. The "Other" category for study AI420-037 contains early discontinuation because of a resistant pathogen, transfer to another hospital, and discontinuation due to possible missed dose of ceftriaxone. The one death in AI420-038 was due to an oral squamous cell carcinoma.

*Reviewer's Comment:* Note that AI420-037 has a higher rate of unable to determine than the other studies (17% for -037 vs. 5% for -002 and 7% for -038). This was most likely due to the fact that all subjects in study AI420-037 were hospitalized and thus this study had a larger percentage of subjects with severe pneumonia. Note that the large number of UTDs in study AI420-037 is more due to "Adverse event", "Other systemic antibiotic", and "Patient request/withdrew consent" rather than due to "Inadequate follow-up."

Table II.7 (from Tables 10.1.1.3 and Tables 10.1.1.4 of BMS study reports for AI420-002, -037 and -038) contains the cure rates by prognostic factors and severity of pneumonia for the evaluable patients. In study AI420-002, gatifloxacin patients had slightly lower response rates than clarithromycin for all levels of prognostic factors except chest x-ray reading of Multilobar Involvement and severe pneumonia. In study AI420-037, gatifloxacin patients had slightly higher response rates for all levels of prognostic factors except in older patients and chest x-ray reading of Multilobar Involvement. In study AI420-038, gatifloxacin patients had slightly lower response rates than levofloxacin patients for all levels of prognostic factors except severe pneumonia.

Older patients on gatifloxacin did better than younger patients in study AI420-002 but worse than younger patients in studies AI420-037 and -038. Subjects without a history of pneumonia in the last 12 months had a higher cure rate than those with a history of pneumonia across all of the 6 treatment arms. This was also true for history of comorbid disease. Subjects with multilobar

involvement on gatifloxacin had a lower cure rate than subjects with a single lobe involvement on gatifloxacin for studies AI420-037 and -038 and had a higher cure rate in study AI420-002. Subjects with severe pneumonia on gatifloxacin had a higher cure rate than those with mild or moderate pneumonia on gatifloxacin in studies AI420-002 and -038. Subjects with mild or moderate on gatifloxacin had higher cure rates than those with severe in study AI420-037.

**Table II.7 Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients**  
**Protocols AI420-002, AI420-037, and AI420-038**

Prognostic Factor/ Subcategory	Number Cured/Evaluable Patients (%)					
	Study AI420-002		Study AI420-037		Study AI420-038	
	Gatifloxacin N = 191	Clarithromycin N = 190	Gatifloxacin N = 104	Ceftriaxone N = 108	Gatifloxacin N = 172	Levofloxacin N = 178
<b>Patient Age</b>						
≤ 65 Years	129/147 (88)	134/149 (90)	50/53 (94)	42/48 (88)	116/128 (91)	114/122 (93)
> 65 Years	40/44 (91)	38/41 (93)	42/51 (82)	50/60 (83)	38/44 (86)	52/56 (93)
<b>History of Pneumonia in Last 12 Months</b>						
Yes	7/11 (64)	15/17 (88)	7/8 (88)	11/14 (79)	13/15 (87)	17/19 (89)
No	162/180 (90)	157/173 (91)	85/96 (89)	81/94 (86)	141/157 (90)	149/159 (94)
<b>History of Comorbid Disease</b>						
Yes	44/52 (85)	41/47 (87)	51/59 (86)	56/67 (84)	52/60 (87)	54/58 (93)
No	125/139 (90)	131/143 (92)	41/45 (91)	36/41 (88)	102/112 (91)	112/120 (93)
<b>Chest X-ray Reading</b>						
Single Lobe	128/147 (87)	134/148 (91)	66/73 (90)	59/71 (83)	111/123 (90)	120/128 (94)
Multilobar	41/44 (93)	38/42 (90)	26/31 (84)	33/37 (89)	43/49 (88)	46/50 (92)
<b>Severity of Pneumonia</b>						
Severe	47/52 (90)	39/45 (87)	64/75 (85)	69/82 (84)	63/69 (91)	53/59 (90)
Mild to Moderate	122/139 (88)	133/145 (92)	28/29 (97)	23/26 (88)	91/103 (88)	113/119 (95)

Table II.8 contains the eradication rates by the most common pathogens found in these studies. The pathogen was assumed eradicated if the subject had either the response of eradicated or presumed eradication. This table is composed of information found in tables 10.1.2 from BMS study reports of AI420-002, -037, and -038. The eradication rates were similar among the treatment groups.

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**Table II.8 Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients Protocols AI420-002, AI420-037 and AI420-038**

Pathogen	Study AI420-002 Number Eradicated/Number Isolated (%)		Study AI420-037 Number Eradicated/Number Isolated (%)		Study AI420-038 Number Eradicated/Number Isolated (%)	
	Gatifloxacin N = 90	Clarithro. N = 94	Gatifloxacin N = 50	Ceftriaxone N = 54	Gatifloxacin N = 92	Levofloxacin N = 81
<u>Typical</u>						
H. influenzae	11/13 (85)	11/15 (73)	7/8 (88)	9/10 (90)	9/9 (100)	12/12 (100)
S. pneumoniae	20/21 (95)	26/26 (100)	17/22 (77)	19/21 (90)	12/14 (86)	13/16 (81)
M. catarrhalis	3/3 (100)	6/6 (100)	3/3 (100)	6/8 (75)	11/11 (100)	8/8 (100)
S. aureus	4/4 (100)	9/10 (90)	7/7 (100)	13/14 (93)	22/24 (92)	12/14 (86)
H. parainfluenzae	5/6 (83)	11/12 (92)	2/2 (100)	2/2 (100)	25/27 (93)	13/13 (100)
<u>Atypical</u>						
M. pneumoniae	28/28 (100)	31/32 (97)	7/7 (100)	4/4 (100)	15/16 (94)	13/13 (100)
L. pneumophila	9/10 (90)	3/4 (75)	3/3 (100)	3/4 (75)	6/6 (100)	4/4 (100)
C. pneumoniae	19/20 (95)	13/17 (76)	5/5 (100)	4/5 (80)	8/8 (100)	10/12 (83)

Relapses were to be assessed in the final follow-up between Days +21 and +28. In study AI420-002, out of the 341 evaluable cures, 294 (86%) had a follow-up within this window. Of these 294 there were 3 subjects who relapsed and all were on gatifloxacin. In study AI420-037, out of 184 evaluable cures, 129 (70%) had a follow-up within this window. Of these 129 there were 3 relapses, 1 in the gatifloxacin arm and two in the ceftriaxone arm. In study AI420-038, out of 320 evaluable cures, 254 (79%) had a follow-up within this window. Of these 254 there were 2 relapses, 1 in the gatifloxacin arm and 1 in the levofloxacin arm.

*Reviewer's comment: If the subjects who relapse were considered as failures, the 95% confidence intervals for the evaluable data sets would be (-11.85, 3.66) for study AI420-002, (-7.0, 16.5) for study -037, and (-11.6, 3.7) for study -038. Overall, the results remained unchanged. These intervals are still within the limit of -15%.*

#### 4. Reviewer's Additional Analyses

##### Covariate Analyses

Analyses by race and gender were conducted. No large treatment differences were seen either within or between treatments by gender in studies AI420-002, AI420-037, and AI420-038. There were some trends seen in the analyses by race, but they are not consistent across studies. Whites had similar cure rates across treatments in all three studies. The evaluable cure rates range from 81% to 93%. In all studies, the Hispanic/Latino evaluable subsets had 100% cure rates. The Hispanic subset, however, is only 9%, 2%, and 4% of the evaluable data set in the 3 studies. In study AI420-002 where blacks make up only 4% of the evaluable data set, blacks had 100% cure rate on gatifloxacin and only 86% cure rate on clarithromycin. In study AI420-037 where blacks make up 19% of the evaluable data set, blacks had 100% cure rates. In study AI420-038 where blacks make up 10% of the evaluable data set, blacks on gatifloxacin had a significantly lower cure rate than blacks on levofloxacin (63% vs. 100%,  $p=0.03$  for the evaluable data set, using an exact method).

### Missing Data Analyses

In the sponsor's analyses, missing data (unable to determine) were treated as failures. Since this is an equivalence trial this method of "imputing" missing values may not be conservative. The true difference may be diluted by a large number of missing values. To examine the robustness of the conclusions with regard to the missing data, a very conservative analysis was conducted. The analysis considered all missing data on gatifloxacin as treatment failures and all missing data on the controls as cures. The 95% confidence intervals calculated using an exact method are given here.

<i>Missing Data Analysis</i>	AI420-002	AI420-037	AI420-038
All Treated Patients	(-17.5%, -2.5%)	(-24.2%, -2.9%)	(-17.9%, -3.2%)
Clinically Eligible	(-15.7%, -0.5%)	(-23.9%, -2.2%)	(-19.0%, -4.1%)

Though none of these confidence intervals fall within the bound of -15%, it does not mean that gatifloxacin is not equivalent to the controls. However, it does signify that the results are not robust enough for this extreme method of imputation. The confidence intervals for study AI420-037 are the widest due to the large percentage of missing data in this study.

### By Center Analyses

There were no centers unduly weighting the results. The large centers showed treatment effects most similar to the mean of all the treatment effects. Mantel-Haenszel confidence intervals with continuity correction were constructed to stratify by center. The results of this analysis are shown in the table below. Note that none of the confidence intervals extend past the limit of -15%.

<i>By Center Analysis</i>	AI420-002	AI420-037	AI420-038
All Treated Patients	(-12.6%, 2.6%)	(-8.6%, 12.7%)	(-10.6%, 3.7%)
Clinically Eligible	(-12.7%, 2.6%)	(-9.4%, 12.2%)	(-12.5%, 2.1%)
Clinically Evaluable	(-11.0%, 4.2%)	(-7.1%, 14.2%)	(-9.5%, 4.8%)

### Relapses and New Infections

Three additional analyses were conducted. One considered relapses and subjects who did not return for a follow-up visit as failures, the second considered subjects with a new respiratory infection as failures and the third combined these two analyses.

Based on the original protocol all subjects should have been assessed for relapse at a late follow-up visit. Many subjects who were considered cured did not have a follow-up visit during the window +21 to +28. Some of these subjects had a test of cure visit before Day +14, the upper end of the original window, and a follow-up after Day +14. However, there were a few subjects that were considered cures that were not seen for any follow-up visit after Day +14. An analysis was conducted that considered all relapses as failures and assumed the worse case scenario that all of these subjects not seen after Day +14 had a relapse. In study AI420-002, 10 subjects did not have a follow-up visit after Day +14. In study AI420-037, 14 subjects did not have a follow-up visit after Day +14. In study AI420-038, 22 subjects did not have a follow-up visit after Day +14. All of the resulting confidence intervals, shown in the table below under "Relapse Analysis", are within the -15% limit for equivalence.

There were a number of patients in all three studies who experienced a new respiratory infection. In a conservative analysis these subjects who were considered cures by the sponsor were changed to failures. Our definition of new respiratory infection included upper and lower respiratory infection, bronchitis, and pneumonia. In study AI420-002, there were 14 cured subjects in the evaluable population with a new respiratory infection (8 on gatifloxacin and 6 on clarithromycin).

In study AI420-037, there were 4 cured subjects in the evaluable population with a new respiratory infection (2 on gatifloxacin and 2 on ceftriaxone). In study AI420-038, there were 3 cured subjects in the evaluable population with a new respiratory infection (2 on gatifloxacin and 1 on levofloxacin). All of the resulting confidence intervals, shown in the table below under "New Infection Analysis", are within the -15% limit for equivalence.

A final global analysis was conducted that treated both relapses (both observed and assumed relapses) and new respiratory infections as failures. The resulting confidence intervals, shown in the table below, for study AI420-037 and -038 are within the -15% limit for equivalence. The confidence interval for study AI420-002 has a lower limit of -16.0%. In this study, gatifloxacin had both a slightly larger number of subjects without a follow-up after Day +14 and a slightly larger number of subjects with a new respiratory infection than clarithromycin.

<i>Evaluable Population</i>			
<i>Relapses/New Infections</i>	AI420-002	AI420-037	AI420-038
Relapse Analysis	(-14.4%, 2.1%)	(-10.3%, 15.4%)	(-8.0%, 9.9%)
New Infection Analysis	(-11.8%, 4.8%)	(-8.1%, 15.6%)	(-12.3%, 3.2%)
Combined Analysis	(-16.0%, 1.6%)	(-11.4%, 14.6%)	(-8.8%, 9.4%)

## 5. Safety

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

There were a total of 323 patients in study AI420-002, 261 patients in study -037 and 270 patients in study -038 who experienced one or more adverse events. In study AI420-002, 166 were on gatifloxacin (76% of the gatifloxacin arm) and 157 were on clarithromycin (73% of the clarithromycin arm). In study AI420-037, 128 (91%) were in gatifloxacin patients and 133 (94%) were in ceftriaxone patients. In study AI420-038, 133 were on gatifloxacin (64% of the gatifloxacin arm) and 137 were on cefuroxime axetil (66% of the levofloxacin arm). A total of 165 subjects in study AI420-002 (81 on gatifloxacin and 88 on clarithromycin), 149 subjects in Study 037 (69 on gatifloxacin and 80 on ceftriaxone), and 125 subjects in study -038 (58 on gatifloxacin and 32 on levofloxacin) were thought to have experienced a drug related adverse event. The most common were nausea, diarrhea, constipation, vomiting, vaginitis, and dizziness. The majority of all the adverse events were considered mild or moderate. In study -002 there were 8 severe drug-related adverse events on gatifloxacin in 002 and 8 severe and 1 very severe adverse events on clarithromycin. In study -037 there were 3 drug-related severe events and 2 very severe events on gatifloxacin and 7 severe events on ceftriaxone. In study -038 there was 5 drug-related severe adverse event on gatifloxacin and none on levofloxacin.

There was 1 death within 30 days of end of treatment and 3 deaths after 30 days in study AI420-002. All four patients were on the clarithromycin arm and their deaths were not thought to be drug related. Due to study -037 being studied in hospitalized patients, the number of deaths was much higher. There were 12 deaths within 30 days of the end of treatment (7 in the gatifloxacin arm and 5 in the ceftriaxone arm). However, none were thought to be study drug related. Five of the deaths on the gatifloxacin arm were thought to be caused from the underlying disease in addition to their primary infection. The other three on the gatifloxacin arm all had underlying COPD. Three additional deaths after Day'+30 occurred in patients from study -037, one in the gatifloxacin arm and 2 in the ceftriaxone arm. In study AI420-038 there was one death within 30 days in the gatifloxacin arm caused by hemorrhaging from an oral squamous cell carcinoma. There was one death on day 31 in the gatifloxacin arm due to a myocardial infarction. There were no deaths on the levofloxacin arm.

There were 23 patients who experienced one or more serious adverse events (16 on gatifloxacin and 7 on clarithromycin) in study AI420-002, 53 patients (29 on gatifloxacin and 24 on ceftriaxone) in study -037 and 24 (16 on gatifloxacin and 8 on levofloxacin) in study -038. In study -002, in 3 of the gatifloxacin patients and 1 of the clarithromycin patients, the events were thought to be study drug related. These serious adverse events in the gatifloxacin patients were nausea, hypoglycemia and bronchospasm. The serious adverse event in the clarithromycin patient was pneumonia. In study -037, 4 gatifloxacin patients and 2 ceftriaxone patients were thought to have had a drug related serious adverse event. These serious adverse events in the gatifloxacin patients were nausea and vomiting, paranoia, confusion and left hemiplegia and possible cerebrovascular accident, and severe bacteremic *H. influenzae* pneumonia. The serious events in the ceftriaxone patients were CHF exacerbation and respiratory failure. In study -038, 2 gatifloxacin patients and no levofloxacin patients were thought to have had a drug related serious adverse event. These events were bradycardia and diabetes.

Fourteen of the gatifloxacin patients and 11 of the clarithromycin patients in study -002, 11 of the gatifloxacin patients and 12 of the ceftriaxone patients in study -037, and 10 of the gatifloxacin and 5 of the levofloxacin patients in study -038 discontinued study drug due to adverse events.

#### **6. Statistical Reviewer's Overall Assessment and Conclusion**

The clinical response for gatifloxacin was slightly lower than for clarithromycin and levofloxacin and slightly higher than for ceftriaxone. Gatifloxacin was shown to be equivalent to the controls in all the populations considered. These results seem fairly robust and suggest that gatifloxacin is similar to the three controls in terms of efficacy.

**APPEARS THIS WAY  
ON ORIGINAL**

### III. ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Two phase III and one phase II studies were conducted for the indication of acute exacerbation of chronic bronchitis; two active controlled blinded studies (AI420-001 and AI420-020) and an open-label non-comparative study (AI420-004). A total of 907 patients were studied; 697 in the controlled studies and 210 in the open-label study. Study AI420-004 was designed to document the activity of gatifloxacin in a respiratory tract infection. Study AI420-001 and -020 were designed to demonstrate the safety and efficacy of gatifloxacin compared to levofloxacin and cefuroxime axetil, respectively, in adults with documented acute exacerbation of chronic bronchitis. The studies had very similar designs and conduct. Only the controlled studies will be discussed in this review. For a complete discussion of study AI420-004 please see the medical officer's review.

#### **Protocol AI420-001: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, COMPARATIVE STUDY OF GATIFLOXACIN VERSUS LEVOFLOXACIN IN THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS**

#### **Protocol AI420-020: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, COMPARATIVE STUDY OF GATIFLOXACIN VERSUS CEFUROXIME AXETIL IN THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS**

##### **1. Objectives and Study Design**

The objective of study AI420-001 and AI420-020 was to establish clinical efficacy and safety of gatifloxacin 400 mg orally once daily for 7 – 10 days compared to an active control of levofloxacin 500 mg once daily for 7 – 10 days and of cefuroxime axetil, 250 mg PO BID for 7 – 10 days in the treatment of acute exacerbation of chronic bronchitis.

Study AI420-001 was conducted at 26 study sites (20 enrolled patients) in the US from October 9, 1997 to June 15, 1998. Study AI420-020 recruited 55 study sites in the US, Argentina, Brazil, Canada, Mexico, Puerto Rico, and South Africa. Thirty-one sites enrolled patients (no sites in Brazil enrolled patients) from August 29, 1997 to June 23, 1998.

These studies were randomized (1:1), double-blind, multi-center, two arm comparative studies. Three hundred sixty patients were enrolled in AI420-001 and 340 were enrolled in AI420-020. Patients were stratified at the time of randomization based on their smoking status (current smokers, including those who quit smoking within 2 months of randomization, and non-smokers). The primary inclusion criteria were the presence of purulent sputum (>25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low power field) and increases in at least two of the following: cough and/or dyspnea, sputum volume, sputum purulence. Patients who were determined to be ineligible for the study after they were enrolled and treated with the study medication were included in the intent-to-treat analyses and removed from the per-protocol analyses.

*Reviewer's comment: The studies used a dynamic randomization algorithm to assign subjects to treatments while ensuring balance between the two treatments within center and by smoking status (Pocock SJ and Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-115). At the present time we do not know of any appropriate analysis that takes this randomization into account. The analyses shown in this report assume that a simple randomization technique was used. It is not known if*

*the results reported in this review are more or less conservative due to the dynamic randomization. Additional details of this issue are given in the Introduction. Note that sites located in Argentina, Mexico, Puerto Rico and South Africa enrolled patients into this study using a permuted block within smoking and center strata randomization.*

The following notation is used to indicate study periods: first day of study drug therapy is Day 1, days on which study drug was administered are Day 1, Day 2, Day 3, etc., pre-treatment days are Day -2, Day -1, etc., and post-treatment days are Day +1, Day +2, etc.. Patients were evaluated pre-treatment, during treatment, end of treatment, post-treatment (Test of Cure visit), and at an extended follow-up. The clinical response was based on the signs and symptoms reported at the Test of Cure visit conducted between Day +5 to Day +18, or earlier for those who discontinued. The Test of Cure visit window was extended from Day +7 to +14 to include any follow-up visit between Day +5 and Day +18. This change was made in the Analysis Plan submitted on June 19, 1998; study unblinding was done on September 17, 1998 for AI420-001 and on September 23, 1998 for AI420-020. The final follow-up was conducted by telephone between Day +21 to Day +28 to assess relapse.

At the Test of Cure visit a clinical response of cured, failure, or unable to determine (UTD) was recorded for each subject. Treatment failures could be assessed anytime after 3 days of treatment. The primary efficacy variable as defined by the sponsor was the clinical response rate at the Test of Cure visit in clinically evaluable patients. The FDA considers analyses based on the intent to treat population as co-primary. The definitions of Cure, Failure, and Unable to Determine given on page 44 of the BMS study report for AI420-001 are shown here:

#### CURED

- All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) have improved or returned to the patient's baseline level with the original therapy alone without need for further antimicrobials; and
- No new signs or symptoms of acute infection were present.

(Note: Baseline is defined as the patient's assessment of their typical/usual condition when free of acute infection)

#### FAILURE

- Signs and symptoms related to the acute infection (cough, dyspnea, sputum production, or sputum purulence) did not improve after 3 days of study therapy; or
- New clinical signs and symptoms of acute infection were present; or
- If present at study entry, fever persisted (i.e., temperature >38.0 C); or
- The patient was removed from the study and placed on alternate antibiotic therapy because of persistent, worsened or new signs and symptoms of acute infection after at least three days of study therapy; or
- Clinical/radiological evidence of pneumonia; or
- Another antibiotic is required for treatment of this acute episode despite the resolution of signs and symptoms.

#### UNABLE TO DETERMINE

- No post-treatment evaluation of signs and symptoms was done (i.e., no Test of Cure Visit); or
- The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the Test of Cure Visit.

Subjects were tested for pre-treatment pathogens from sputum specimens. Each pre-treatment pathogen was then assigned a bacteriologic response at the end of study based on either a post-

treatment culture or the subject's clinical response. The bacteriologic responses were: Eradicated based on a post-treatment culture, Presumed Eradicated if there was not a post-treatment culture but the subject was clinically cured, Persisted based on a post-treatment culture, and Presumed Persisted if there was not a post-treatment culture but the subject was a clinical failure.

Four data sets were of interest in the analyses; All Treated patients data set is the intent to treat data set, Eligible patients data set is a modified intent to treat data set, Clinically Evaluable patients data set is the per-protocol data set, and Microbiologically Evaluable patients data set includes patients in the clinically evaluable data set who had a pathogen isolated pre-treatment. The exact definitions of the data sets from page 53 of the study report for AI420-001 are given here:

- **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:
  - Having evidence of purulence in an adequate pre-treatment sputum sample (>25 PMN per LPF – the original inclusion criteria required < 10 epithelial cells as well, but this criteria was relaxed based on accepted criteria of sputum purulence).
  - Having two or more of the following signs/symptoms of AECB:
    - increased dyspnea/cough;
    - increased sputum production;
    - increased sputum purulence.
- **Clinically Evaluable Patients:** All Eligible Patients who:
  - Had a duration of dosing of at least five days (at least 3 days for treatment failures);
  - Had a post-treatment clinical assessment within the Day +5 to Day +18 window for the Test of Cure Visit (except for failures); and
  - 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.

Included in the criteria for "Eligible Patients" for AI420-020 was " - Having a pre-treatment radiography that did not show pneumonia."

*Reviewer's comment: The definition of sputum purulence was relaxed to allow patients to meet inclusion criteria regardless of epithelial cell count. This was stated in the Analysis Plan submitted on June 19, 1998. This changed only the study analysis. The conduct of the study was not changed. The results of analyses excluding subjects with epithelial cell count > 10 are included in Section 4.*

## 2. Study Population and Baseline Demographics

### *Study AI420-001*

A total of 360 patients were enrolled in 20 study centers. Of the 360 subjects enrolled in the study, 358 patients were treated; 179 received gatifloxacin and 179 received levofloxacin. Two subjects (1 on gatifloxacin and 1 on levofloxacin) were labeled as not taking any study medication and were removed from all of the data sets. Three hundred thirty-six patients (94% of all treated patients) were considered in the Eligible data set. Two hundred ninety six patients (83% of all treated patients) were considered Clinically Evaluable (145 on gatifloxacin and 151 on levofloxacin). Two hundred eight patients were microbiologically evaluable. Table III.1

below contains the specific information on the protocol violations/reasons for exclusions (from Table 8.1B BMS study report for AI420-001).

**Study AI420-020**

A total of 340 patients were enrolled in 31 study centers. Of the 340 subjects enrolled in the study, 339 patients were treated; 169 received gatifloxacin and 170 received cefuroxime axetil. One subject (on cefuroxime axetil) was labeled as not taking any study medication and was removed from all of the data sets. Three hundred nine patients (91% of all treated patients) were considered in the Eligible data set. Two hundred eighty four patients (84% of all treated patients) were considered Clinically Evaluable (145 on gatifloxacin and 139 on cefuroxime axetil). One hundred thirty patients were microbiologically evaluable. Table III.1 below contains the specific information on the protocol violations/reasons for exclusions (from Table 8.1B BMS study report for AI420-020).

**Table III.1 Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients  
Protocol AI420-001 and AI420-020**

Reason	Study AI420-001 Number of Patients (%)			Study AI420-020 Number of Patients (%)		
	Gatifloxacin N = 179	Levofloxacin N = 179	Total N = 358	Gatifloxacin N = 169	Cefuroxime N = 170	Total N = 339
<b>Treated</b>	179	179	358	169	170	339
<b>Eligible</b>	167 (93)	169 (94)	336 (94)	156 (92)	153 (90)	309 (91)
<b>Ineligible</b>	12 (7)	10 (6)	22 (6)	13 (8)	17 (10)	30 (9)
<u>Reason Ineligible:</u>						
Did Not Have Diagnosis of Chronic Bronchitis	-	-	-	-	1 (<1)	1 (<1)
No Pre-treatment Purulent Sputum Specimen	9 (5)	8 (4)	17 (5)	11 (7)	13 (8)	24 (7)
Evidence of Pneumonia on Pre-treatment X-ray	1 (<1)	2 (1)	3 (<1)	1 (<1)	1 (<1)	2 (<1)
Other	2 (1)	-	2 (<1)	1 (<1)	2 (1)	3 (<1)
<b>Clinically Evaluable</b>	145 (81)	151 (84)	296 (83)	145 (86)	139 (82)	284 (84)
<b>Clinically Unevaluable</b>	34 (19)	28 (16)	62 (17)	24 (14)	31 (18)	55 (16)
<u>Reason Unevaluable:</u>						
No Test of Cure Visit	14 (8)	13 (7)	27 (8)	7 (4)	10 (6)	17 (5)
Ineligible	12 (7)	10 (6)	22 (6)	13 (8)	17 (10)	30 (9)
Insufficient Dosage	2 (1)	4 (2)	6 (2)	2 (1)	1 (<1)	3 (<1)
Other Antibiotic Received	4 (2)	1 (<1)	5 (1)	1 (<1)	2 (1)	3 (<1)
Other	2 (1)	-	2 (<1)	1 (<1)	1 (<1)	2 (<1)
<b>Microbiologically Evaluable</b>	107 (60)	101 (56)	208 (58)	70 (41)	60 (35)	130 (38)
<b>Microbiologically Unevaluable</b>	72 (40)	78 (44)	150 (42)	99 (59)	110 (65)	209 (62)
<u>Reason Unevaluable:</u>						
Clinically Unevaluable	25 (14)	16 (9)	41 (11)	14 (8)	12 (7)	26 (8)
No Pre-treatment Pathogen Resistant Pathogen	46 (26)	62 (35)	108 (30)	78 (46)	92 (54)	170 (50)
Resistant Pathogen	1 (<1)	-	1 (<1)	7 (4)	6 (4)	13 (4)

There were not large differences in the demographic characteristics gender, race, age and weight between the two treatment groups in either study. In study AI420-001, 41% were female (47% gatifloxacin and 35% levofloxacin), 72% were white, 25% black, and 3% Hispanic. The mean age was 51 years with a range of 18 to 85 years and the mean weight was 80.2 kg with a range of 37.6 to 154.4 kg. In study AI420-020, 45% were female, (44% in gatifloxacin and 46% in cefuroxime axetil), 61% were white, 15% black, and 19% Hispanic. The mean age was 55 years with a range of 19 to 90 and the mean weight was 74.7 kg with a range of 34.0 to 136.1 kg. There were no large differences in recorded medical history, use of antimicrobial medications, prognostic values, or pre-treatment signs and symptoms in either study.

### 3. Applicant's Analyses and Results

It was stated in the study reports that gatifloxacin would be considered no worse than levofloxacin or cefuroxime axetil if the 95% confidence interval around the difference in cure rates did not extend beyond  $\delta\%$  in favor of the comparator, where  $\delta$  equals 20 if the largest observed cure rate is between 70 and 79%, 15 if the cure rate is between 80 and 89%, and 10 if the cure rate is 90% or larger. The confidence intervals were constructed using the DerSimonian and Laird method using smoking status as a stratification factor, as pre-specified in the analysis plan.

*Reviewer's comment:* Based on the rule stated above, the limit for equivalence would be 10% for study AI420-001 and 15% for study AI420-020. However, in line with the recent July 1998 Anti-Infective Advisory Committee meeting, we will consider the limit of equivalence to be independent of observed response. Since 15% was discussed and agreed upon by the FDA in reference to all recently submitted gatifloxacin protocols, we will use 15% in determining equivalence in this study.

*Reviewer's comment:* The DerSimonian and Laird method (DerSimonian R and Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-188) allows for differences between the cure rates based on smoking status and calculates a common difference between treatments for smokers and non-smokers. It considers the differences in results across strata as random error that is accounted for in the estimate of the variability. However, it is not completely clear if differences between smokers and nonsmokers should be considered random, or if it is suitable to use this type of model with only 2 strata. The magnitude of the difference in treatment effect seen between smokers and nonsmokers may indicate that the difference should not be treated as pure variability and that it may not be sensible to estimate a common difference. In this case it is perhaps best to analyze the treatment effect by strata rather than in pooling the values. A test for homogeneity is conducted prior to calculating the DerSimonian and Laird confidence interval to look for consistency across stratification factor (smoking status).

#### Study AI420-001

Table III.2 reports the study AI420-001 results for clinical response for the all treated patients (AT), eligible (Elig), clinically evaluable (Eval), and microbiologically evaluable (M.Eval) data sets. The cure rates for levofloxacin were slightly higher than for gatifloxacin in all four data sets. The confidence intervals for the all treated patients and evaluable data sets were just within the 15% limit. However, the eligible data set had a lower confidence limit of -17.6.

**Table III.2 BMS study results AI420-001**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Levofloxacin			
	AT n = 179	Elig n = 167	Eval n = 145	M.Eval n = 107	AT n = 179	Elig n = 169	Eval n = 151	M.Eval n = 101
Cured	140 (78)	129 (77)	127 (88)	94 (88)	150 (84)	141 (83)	139 (92)	93 (92)
Failure	18 (10)	18 (11)	18 (12)	13 (12)	12 (7)	12 (7)	12 (8)	8 (8)
Unable to Determine	21 (12)	20 (12)	N/A	N/A	17 (9)	16 (9)	N/A	N/A

95% Confidence interval for the difference in Cure rate stratified by smoking status:

- AT (-14.9, 3.4)
- Elig (-17.6, 4.5)
- Eval (-14.6, 6.2)
- M. Eval (-10.7, 3.3)

*Reviewer's comments: There is a large difference in treatment effects between smokers and nonsmokers. There is only a negligible difference between gatifloxacin and levofloxacin in smokers (0% for evaluable, -1% for eligible, -2% for all treated, and -3% for microbiologically evaluable). However, the difference between gatifloxacin and levofloxacin for non-smokers was quite large (-11% for evaluable, -13% for eligible, -11% for all treated and -7% for microbiologically evaluable). This difference is due to lower cure rates for nonsmokers on gatifloxacin. Despite this difference in treatment effect over the stratification variable, the test for homogeneity was not rejected, meaning that this difference was not statistically significant. This lack of significance, however, could be more a function of sample size and power than the lack of a true difference. The table below contains the cure rates and 95% confidence intervals by smoking status. The confidence intervals are calculated using an exact method.*

Study AI420-001 By Smoking Status	Number Cured/Number of Patients (%)		95% C.I.*
	Gatifloxacin	Levofloxacin	
<b>All Treated Patients</b>			
Current Smokers	85/106 (80)	86/105 (82)	(-15.0%, 10.1%)
Non-smokers	55/73 (75)	64/74 (86)	(-26.5%, 4.1%)
<b>Clinically Eligible</b>			
Current Smokers	79/99 (80)	78/96 (81)	(-15.3%, 11.1%)
Non-smokers	50/68 (74)	63/73 (86)	(-29.1%, 2.5%)
<b>Clinically Evaluable</b>			
Current Smokers	78/83 (94)	77/82 (94)	(-10.9%, 11.2%)
Non-smokers	49/62 (79)	62/69 (90)	(-27.3%, 4.1%)
<b>Micro. Evaluable</b>			
Current Smokers	58/62 (94)	52/54 (96)	(-16.8%, 10.4%)
Non-smokers	36/45 (80)	41/47 (87)	(-27.3%, 11.9%)

*All the confidence intervals for all treated and evaluable current smokers are within the -15% limit despite the reduced sample size. The confidence intervals for non-smokers do not fall within the -15% limit for any of the data sets. This is both due to the reduced sample sizes and the large observed treatment differences.*

**Study AI420-020**

Table III.3 reports study AI420-020 results for clinical response for the all treated patients (AT), eligible (Elig), clinically evaluable (Eval), and microbiologically evaluable (M. Eval) data sets.

The cure rates for cefuroxime axetil were slightly lower than for gatifloxacin in all four data sets. The confidence intervals for all four data sets were within the 15% limit.

**Table III.3 BMS study results AI420-020**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Cefuroxime axetil			
	AT n = 169	Elig n = 156	Eval n = 145	M. Eval n = 70	AT n = 170	Elig n = 153	Eval n = 139	M. Eval n = 60
Cured	136 (80)	126 (81)	124 (86)	57 (81)	133 (78)	121 (79)	115 (83)	48 (80)
Failure	22 (13)	21 (13)	21 (14)	13 (19)	29 (17)	25 (16)	24 (17)	12 (20)
Unable to Determine	11 (7)	9 (6)	N/A	N/A	8 (5)	7 (5)	N/A	N/A
95% Confidence interval for the difference in Cure rate stratified by smoking status:					AT (-6.3, 10.7) Elig (-6.9, 10.6) Eval (-4.8, 11.4) M.Eval (-11.3, 15.6)			

*Reviewer's comment: The differences between the treatment effects were similar for smokers and nonsmokers. However, the cure rates for smokers were higher than the cure rates for nonsmokers in both treatment groups. The table below contains the cure rates and 95% confidence intervals by smoking status. The confidence intervals are calculated using an exact method.*

Study AI420-020 By Smoking Status	Number Cured/Number of Patients (%)		
	Gatifloxacin	Cefuroxime axetil	95% C.I. <sup>a</sup>
<b>All Treated Patients</b>			
Current Smokers	74/87 (85)	69/84 (82)	(-10.5%, 16.9%)
Non-smokers	62/82 (76)	64/86 (74)	(-13.3%, 16.9%)
<b>Clinically Eligible</b>			
Current Smokers	67/78 (86)	63/76 (83)	(-11.5%, 17.6%)
Non-smokers	59/78 (76)	58/77 (75)	(-15.2%, 16.1%)
<b>Clinically Evaluable</b>			
Current Smokers	66/72 (92)	60/69 (87)	(-8.8%, 19.1%)
Non-smokers	58/73 (79)	55/70 (79)	(-14.7%, 17.3%)
<b>Micro. Evaluable</b>			
Current Smokers	29/34 (85)	29/35 (83)	(-18.7%, 27.6%)
Non-smokers	28/36 (78)	19/25 (76)	(-22.9%, 29.4%)

*All the confidence intervals for all treated and evaluable data sets are within the -15% limit despite the reduced sample size. The confidence intervals the microbiologically evaluable data set do not fall within the -15% limit due to the greatly reduced sample size.*

*Gatifloxacin had a higher cure rate in North America (US and Canada) than in "other countries" (89% versus 80%, clinically evaluable patients).*

Table III.4 (from Table 10.3.1.2 of BMS Q01 study report and Table 10.3.2 of BMS 020 study report) gives the reasons why clinical responses were unable to determine in the eligible patients. Note that in the analyses of the all treated patients data set and the eligible data set, subjects whose responses were unable to determine were considered failures in the analyses.

**Table III.4 Reason Clinical Response is Unable to Determine, Clinically Eligible Patients Protocol AI420-001 and AI420-020**

Reason	Study AI420-001 Number of Patients (%)			Study AI420-020 Number of Patients (%)		
	Gatifloxacin N = 167	Levofloxacin N = 169	Total N = 336	Gatifloxacin N = 156	Cefuroxime N = 153	Total N = 309
<b>Number of Responses Unable to Determine</b>						
Inadequate Follow-up	20 (12)	16 (9)	36 (11)	9 (6)	7 (5)	16 (5)
Adverse Event Prior to Assessment	10 (6)	8 (5)	18 (5)	3 (2)	2 (1)	5 (2)
Other Systemic Antibiotic Needed for Reason Other than the Infection Under Study	7 (4)	5 (3)	12 (4)	4 (3)	1 (1)	5 (2)
Inadequate Therapy	3 (2)	1 (1)	4 (1)	1 (1)	2 (1)	3 (1)
Received other antibiotic	-	2 (1)	2 (1)	-	1 (1)	1 (<1)
Patient Unblinded	-	-	-	1 (1)	-	1 (<1)
	-	-	-	-	1 (1)	1 (<1)

Table III.5 (from BMS study report for AI420-001 table 10.1.1.4 and study report for AI420-020 table 10.1.1.4) contains the cure rates by prognostic factors for the evaluable patients. In study 001, gatifloxacin patients had slightly lower response rates than levofloxacin within exacerbation type, duration of current episode and pre-treatment systemic corticosteroid use. Within these prognostic factors, patients with shorter duration of current episode and no pre-treatment use of systemic corticosteroids had slightly higher cure rates. The most striking difference in cure rates was seen in both current smoking status and history of smoking. Patients who were currently non-smokers and those with no history of smoking status and who were randomized to gatifloxacin had a lower cure rate. Current smokers had a cure rate of 94% on both levofloxacin and gatifloxacin. Non-smokers randomized to levofloxacin had a cure rate of 90%, while those randomized to gatifloxacin had a cure rate of 79%. A similar pattern is also seen with history of smoking. In study -020, no strong pattern was seen with any of the prognostic factors except that both non-smokers and those without a history of smoking had lower cure rates than smokers on both treatments.

*Reviewer's comment: These large differences between smokers and non-smokers were not seen in the open-label study, AI420-004. In that study the cure rate for smokers was 89% and for non-smokers was 87%. The cure rate for those with a history of smoking was 89% and without was 83%.*

Table III.6 contains the eradication rates by the most common pathogens found in these studies. The pathogen was assumed eradicated if the subject had either the response of eradicated or presumed eradication. This table is composed of information found in tables 10.2.2 from BMS study report of AI420-001 and AI420-020. The eradication rates were higher in study -001, as were the clinical cure rates for the evaluable data sets.

**Table III.5 Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients Protocol AI420-001 and AI420-020**

Prognostic Factor/ Subcategory	Study AI420-001 Number Cured/Evaluable Patients (%)			Study AI420-020 Number Cured/Evaluable Patients (%)		
	Gatifloxacin N = 145	Levofloxacin N = 151	Total N = 296	Gatifloxacin N = 145	Cefuroxime N = 139	Total N = 284
<b>Exacerbation Type</b>						
Type I	112/127 (88)	122/132 (92)	234/259 (90)	108/125 (86)	97/120 (81)	205/245 (84)
Type II	15/17 (88)	17/19 (89)	32/36 (89)	16/20 (80)	18/19 (95)	34/39 (87)
<b>Duration of Current Episode</b>						
0 - 7 Days	76/83 (92)	86/91 (95)	162/174 (93)	58/67 (87)	53/65 (82)	111/132 (84)
>7 Days	49/60 (82)	50/57 (88)	99/117 (85)	63/74 (85)	59/70 (84)	122/144 (85)
Not Recorded	2/2 (100)	3/3 (100)	5/5 (100)	3/4 (75)	3/4 (75)	6/8 (75)
<b>Pre-treatment Systemic Corticosteroid Use</b>						
Yes	8/10 (80)	12/14 (86)	20/24 (83)	14/17 (82)	13/15 (87)	27/32 (84)
No	119/135 (88)	127/137 (93)	246/272 (90)	110/128 (86)	102/124 (82)	212/252 (84)
<b>Current Smoking Status</b>						
Smoker	78/83 (94)	77/82 (94)	155/165 (94)	66/72 (92)	60/69 (87)	126/141 (89)
Non-Smoker	49/62 (79)	62/69 (90)	111/131 (85)	58/73 (79)	55/70 (79)	113/143 (79)
<b>History of Smoking</b>						
Yes	111/124 (90)	123/135 (91)	234/259 (90)	103/118 (87)	101/122 (83)	204/240 (85)
No	16/21 (76)	16/16 (100)	32/37 (86)	21/27 (78)	14/17 (82)	35/44 (80)

**Table III.6 Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients Protocol AI420-001 and Protocol AI420-020**

Pathogen	Study AI420-001 Number Eradicated/Number Isolated (%)			Study AI420-020 Number Eradicated/Number Isolated (%)		
	Gatifloxacin	Levofloxacin	Total	Gatifloxacin	Cefuroxime	Total
<b>Total</b>	132/141 (94)	129/137 (94)	261/278 (94)	73/84 (87)	54/70 (77)	127/154 (82)
H. influenzae	26/26 (100)	21/21 (100)	47/47 (100)	17/20 (85)	17/23 (74)	34/43 (79)
M. catarrhalis	34/36 (94)	24/27 (89)	58/63 (92)	19/23 (83)	8/9 (89)	27/32 (84)
H. Parainfluenzae	13/15 (87)	21/22 (95)	34/37 (92)	5/7 (71)	5/7 (71)	10/14 (71)
S. pneumoniae	13/13 (100)	15/17 (88)	28/30 (93)	9/9 (100)	5/9 (56)	14/18 (78)
S. aureus	22/26 (85)	24/25 (96)	46/51 (90)	8/8 (100)	11/12 (92)	19/20 (95)

The majority of the all treated subjects took the study medication for either 7 or 10 days. In study AI420-001 26% of patients took their medication for 7 days and 65% took it for 10 days. In study AI420-020 13% took their medication for 7 days and 79% took it for 10 days. The percentages were similar between treatment group. A larger percentage of subjects took 10 days of study medication on study -020 than -001. Ninety-two percent of patients in -001 and 97% in -020 took seven or more days of study medication.

One hundred percent of cures in study AI420-001 and 99% of cures in study -020 had a late follow-up to obtain information on relapse. Of those with a follow-up visit, 94% on gatifloxacin and 95% on levofloxacin in study -001 had a sustained cure and 96% on gatifloxacin and 100% on cefuroxime axetil in study -020 had a sustained cure.

*Reviewer's comment: If the subjects who relapse were considered as failures, the 95% confidence intervals for the evaluable data set would be (-13.02, 2.85) for study -001 and (-7.92, 8.83) for study -020. These intervals are still within the limit of -15%.*

#### 4. Reviewer's Additional Analyses

##### Covariate Analysis

Analyses by age, race and gender were conducted. No large treatment differences were seen either within or between treatments by age group or gender. However, the analyses on race showed that blacks had a very high cure rate across all treatments. Out of a total of 58 subjects on gatifloxacin, 38 on levofloxacin, and 22 on cefuroxime axetil in the evaluable data sets, there were only 2 failures, which gives an overall cure rate of 98%. Correspondingly in whites, out of a total of 186 on gatifloxacin, 107 on levofloxacin, and 90 on cefuroxime axetil in the evaluable data set, there were 65 failures, which gives an overall cure rate of 83%. Note that in the evaluable data set 92% of black are smokers who tend to have a higher cure rate than non-smokers. The percentage of whites that are smokers in the evaluable data set is 43%. This pattern in cure rates for black and whites can also be seen in the open label study (AI420-004). The Hispanic/Latino population (10% of the study population) had an overall cure rate for the evaluable subjects of 90% and smoking rate of 57%.

##### Missing Data Analysis

In the sponsor's analyses, missing data (unable to determine) were treated as failures. Since this is an equivalence trial this method of "imputing" missing values may not be conservative. The true difference may be diluted by a large number of missing values. To examine the robustness of the conclusions with regard to the missing data, a very conservative analysis was conducted. The analysis considered all missing data on gatifloxacin as treatment failures and all missing data on the controls as cures. The 95% confidence intervals calculated using the DerSimonian and Laird method are given here.

<i>Missing Data Analysis</i>	AI420-001	AI420-020
All Treated Patients	(-22.1%, -8.1%)	(-10.7%, 5.2%)
Clinically Eligible	(-23.0%, -8.3%)	(-11.0%, 5.5%)

Study AI420-020 has very robust results. Both the lower bounds remain above -15%. This is in part due to the small percentage of missing data in this study (6%). Though none of the confidence intervals for study AI420-001 fall within the bounds of -15%, it does not mean that gatifloxacin is not equivalent to levofloxacin. However, it does signify that the results are not robust enough for this extreme method of imputation. The percentage of subjects with a clinical response of unable to determine in AI420-001 is 11%.

##### By Center Analysis

There were no centers unduly weighting the results. The large centers showed treatment effects most similar to the mean of all the treatment effects. Mantel-Haenszel confidence intervals with continuity correction were constructed to stratify by center. The results of this analysis are shown in the table below. Note that none of the confidence intervals extend past the limit of -15%.

<i>By Center Analysis</i>	AI420-001	AI420-020
All Treated Patients	(-13.5%, 3.0%)	(-5.6%, 11.4%)
Clinically Eligible	(-14.9%, 2.3%)	(-6.4%, 11.4%)
Clinically Evaluable	(-11.4%, 3.4%)	(-6.5%, 11.1%)

#### Additional Analyses on Smoking Status

BMS conducted an extensive analysis to attempt to assess the differences in cure rates observed in smokers and nonsmokers. The following table contains percentages of patients with different prognostic factors by smoking status and treatment for the two studies. It was found that non-smokers are generally at higher risk for failure based on the prognostic factors. A larger percentage of non-smokers than smokers are greater than 65, have a history of asthma, are taking concomitant medications, and are using steroids.

<i>Study AI420-001</i>	Current Smokers		Non-Smokers	
	<u>Gatifloxacin</u>	<u>Levofloxacin</u>	<u>Gatifloxacin</u>	<u>Levofloxacin</u>
Age >= 65 years	10%	6%	47%	51%
History of Asthma	14%	15%	31%	33%
Concomitant drug	24%	23%	58%	68%
Steroid Use	10%	9%	42%	46%

  

<i>Study AI420-020</i>	Current Smokers		Non-Smokers	
	<u>Gatifloxacin</u>	<u>Cefuroxime axetil</u>	<u>Gatifloxacin</u>	<u>Cefuroxime axetil</u>
Age >= 65 years	14%	13%	49%	59%
History of Asthma	7%	17%	21%	10%
Concomitant drug	37%	35%	73%	71%
Steroid Use	22%	12%	44%	41%

BMS also conducted logistic regression analyses to examine the effect of smoking status on cure, adjusting for a number of prognostic factors. In studies AI420-001 and -002, when treatment and smoking status were alone in the model, smoking status was statistically significant. However, in models that also adjusted for other prognostic factors, smoking status was no longer significant and the magnitude of its affect was diminished.

The only conclusion from this analysis is that non-smokers are at higher risk for failure due to confounding factors. This can be seen in the cure rates by smoking status in both treatment groups in study -020 but only in the gatifloxacin treatment group in study -001.

*Reviewer's comment: The following analyses use data sets defined by the medical officer. Details are given with the analyses.*

#### Revised Definition of Cured

A sensitivity analysis was conducted using a revised definition of cured. A subject's response was changed to failure if the subject was "improved" on the Test of Cure visit on the major signs and symptoms of AECB, but was not "resolved" by the follow-up visit. The major signs and symptoms were increased sputum, increased cough, and increased dyspnea. Tables III.7 and III.8 give the results of the analyses using this definition of cured for -001 and -020. In study -001 the cure rates for levofloxacin remained slightly larger than the cure rates for gatifloxacin and the confidence intervals changed slightly. In study -020 the cure rates for gatifloxacin and cefuroxime axetil were very similar as they were in the original analysis. However, the confidence intervals are much wider for this analysis.

**Table III.7 Revised definition of cured for Study 001**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Levofloxacin			
	AT n = 179	Elig n = 167	Eval n = 145	M. Eval n = 107	AT n = 179	Elig n = 169	Eval n = 151	M. Eval n = 101
Cured	110 (61)	103 (62)	102 (70)	77 (72)	122 (68)	114 (67)	113 (75)	80 (79)
Failure	48 (27)	44 (26)	43 (30)	30 (28)	40 (22)	39 (23)	38 (25)	21 (21)
Unable to Determine	21 (12)	20 (12)	N/A	N/A	17 (9)	16 (9)	N/A	N/A
95% Confidence interval for the difference in Cure rate stratified by smoking status:					AT (-16.4, 3.2) Elig (-15.9, 4.3) Eval (-13.8, 5.6) M. Eval (-17.7, 3.4)			

**Table III.8 Revised definition of cured for Study 020**

Clinical Response	Number (%) of Patients							
	Gatifloxacin				Cefuroxime axetil			
	AT n = 169	Elig n = 156	Eval n = 145	M. Eval n = 70	AT n = 170	Elig n = 153	Eval n = 139	M. Eval n = 60
Cured	97 (57)	90 (58)	88 (61)	40 (57)	99 (58)	88 (58)	82 (59)	33 (55)
Failure	61 (36)	57 (37)	57 (39)	30 (43)	63 (37)	58 (38)	57 (41)	27 (45)
Unable to Determine	11 (7)	9 (6)	N/A	N/A	8 (5)	7 (5)	N/A	N/A
95% Confidence interval for the difference in Cure rate stratified by smoking status:					AT (-15.0, 12.9) Elig (-18.9, 19.5) Eval (-19.2, 23.3) M. Eval (-12.7, 20.9)			

*Reviewer's comment: The confidence intervals for study AI420-020 extended well past the limit of -15% despite very small differences in overall cure rate for the 4 data sets (-1%, 0%, 2%, and 2%). As stated above, these confidence intervals were constructed using the DerSimonian and Laird method and take smoking status into account. The test for homogeneity for the DerSimonian and Laird Confidence intervals gave a p-value of 0.055 for the evaluable data set suggesting a difference in treatment effects for smokers and nonsmokers. Smokers have higher cure rates for gatifloxacin and nonsmokers have higher cure rates for cefuroxime axetil. For the all treated patients data set, the difference in cure rates for smokers is 6% and for nonsmokers is -8%. For the eligible patients data set, the difference in cure rates for smokers is 10% and for nonsmokers is -10%. For the evaluable patients data set, the difference in cure rates for smokers is 13% and nonsmokers is -9%. For the microbiologically evaluable patients data set, the difference in cure rates for smokers is 5% and nonsmokers is 3%. The confidence intervals reported for 020 are quite wide due to this large difference between smokers and nonsmokers. The DerSimonian and Laird confidence intervals treat that difference as a large variability in treatment effect and incorporate that variability into the variability of the confidence interval.*

*The 95% confidence intervals by smoking status using an exact method rather than the DerSimonian and Laird method are given here. The confidence intervals for current smokers are*

well within the limit of -15% for all treated, eligible and clinically evaluable data sets, despite the reduced sample size. However, the confidence intervals for non-smokers are not within the -15% limit.

Study A1420-020 By Smoking Status	Number Cured/Number of Patients (%)		95% C.I. <sup>a</sup>
	Gatifloxacin	Cefuroxime axetil	
<b>All Treated Patients</b>			
Current Smokers	60/87 (69)	53/84 (63)	(-9.3%, 21.6%)
Non-smokers	37/82 (45)	46/86 (53)	(-24.6%, 7.1%)
<b>Clinically Eligible</b>			
Current Smokers	56/78 (72)	47/76 (62)	(-6.2%, 26.3%)
Non-smokers	34/78 (44)	41/77 (53)	(-26.7%, 6.7%)
<b>Clinically Evaluable</b>			
Current Smokers	55/72 (76)	44/69 (64)	(-4.0%, 29.7%)
Non-smokers	33/73 (45)	38/70 (54)	(-26.8%, 7.8%)
<b>Micro. Evaluable</b>			
Current Smokers	23/34 (68)	22/35 (63)	(-18.2%, 31.6%)
Non-smokers	17/36 (47)	11/25 (44)	(-22.6%, 30.7%)

The reason that these differences are seen in this analysis is that the percentage of cures who were only "improved" rather than "resolved" were higher in gatifloxacin's nonsmokers than in gatifloxacin's smokers (14% and 17% for evaluable smokers and 29% and 43% for evaluable non-smokers in 001 and 020). This pattern can also be seen in the levofloxacin treatment arm in 001 (13% for smokers and 26% for nonsmokers) and less noticeably in cefuroxime axetil's treatment arm in 020 (27% for smokers and 31% for nonsmokers).

#### Analyses Using Original Definition of Eligible

Two additional analyses were conducted. The first considered subjects with epithelial cell count greater than 10 as ineligible, as stated in the protocol. The sample sizes decreased by 11% for 001 and 9% for 020. Qualitatively, the conclusions are similar to the BMS analysis, however the confidence intervals are slightly wider due to the decrease in sample size. For study -001 evaluable data set, the cure rate for gatifloxacin was 87% and for levofloxacin it was 91% with a 95% confidence interval on the difference of (-16.3%, 9.1%). For study -020 evaluable data set, the cure rate for gatifloxacin was 85% and for cefuroxime axetil was 82% with a 95% confidence interval on the difference of (-5.6, 11.8).

The second analyses combined the two previous analyses. It considered the definition of cured to exclude those who were not resolved on the primary signs and symptoms by the Test of Cure or follow-up and it considered subjects with epithelial cell count greater than 10 as ineligible. The conclusions are qualitatively the same as the revised definition of cured analysis (Table III.8 and III.9). For study -001 evaluable data set, the cure rate for gatifloxacin was 71% and for levofloxacin it was 75% with a 95% confidence interval on the difference of (-15.7%, 8.4%). For study -020 evaluable data set, the cure rate for gatifloxacin was 58% and for cefuroxime axetil it was 57% with a 95% confidence interval on the difference of (-24.9%, 24.9%). This wide confidence interval is due to the large differences in treatment effects for smokers and non-smokers, as discussed above. The differences in treatment effect between smokers and nonsmokers are included as variability in the construction of the DerSimonian and Laird confidence intervals.

## 5. Safety

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

There were a total of 202 patients in study AI420-001 and 162 patients in study AI420-020 who experienced one or more adverse events. In study -001, 107 were on gatifloxacin (60% of the gatifloxacin arm) and 95 were on levofloxacin (53% of the levofloxacin arm). In study -020, 87 were on gatifloxacin (51% of the gatifloxacin arm) and 75 were on cefuroxime axetil (44% of the cefuroxime axetil arm). A total of 110 subjects in study -001 (60 on gatifloxacin and 50 on levofloxacin) and 89 subjects in study -020 (50 on gatifloxacin and 39 on cefuroxime axetil) were thought to have experienced a drug related adverse event. The most common were nausea, diarrhea, vaginitis, and dizziness. More than half of all the adverse events were considered mild. There were 5 severe adverse events on gatifloxacin in -001 and 4 on levofloxacin. In study -020 there was one severe adverse event on gatifloxacin and one on cefuroxime axetil. There were no very severe adverse events in either study.

There were 2 deaths within 30 days of end of treatment in study -020. Both patients were on the gatifloxacin arm and neither death was thought to be associated with gatifloxacin. One patient died of a myocardial infarction after 5 days of gatifloxacin therapy and one patient died of underlying COPD after withdrawing from the study and receiving ciprofloxacin.

There were 11 patients who experienced one or more serious adverse events (4 on gatifloxacin and 7 on levofloxacin) in study -001 and 10 (7 on gatifloxacin and 3 on cefuroxime axetil) in study -020. However, none were thought to be study drug related.

Twelve (7%) of the gatifloxacin patients and 9 (6%) of the levofloxacin patients in study -001 and 4 (2%) of the gatifloxacin patients and 1 (1%) of the cefuroxime axetil patients in study -020 discontinued study drug due to adverse events. The primary reasons for discontinuations were gastrointestinal and central nervous system events

## 6. Statistical Reviewer's Overall Assessment and Conclusion

The clinical response for gatifloxacin was slightly lower than for levofloxacin and slightly higher than for cefuroxime axetil. The sponsor's confidence intervals for the all treated patients and the clinically evaluable data sets are just within the limit for equivalence for study AI420-001 and well within the limit for AI420-020. There were differences seen in cure rate for smokers and nonsmokers. Nonsmokers on gatifloxacin and cefuroxime axetil had lower cure rates than smokers. However despite the differences, the results for smokers are quite robust and show equivalence between the two treatments in both studies. The results for non-smokers are less robust; equivalence is shown in study -020 but not in -001. Note that these studies were not powered to detect equivalence in these subgroups.

Overall, in both study AI420-001 and -020 gatifloxacin was shown to be equivalent to the controls in both the all treated and the clinically evaluable data sets. These results seem fairly robust and suggest that gatifloxacin is similar to the two controls in terms of efficacy.

## **IV. ACUTE SINUSITIS**

Three studies were conducted for the indication of sinusitis; an open-label non-comparative study (AI420-007) and two active-controlled, blinded studies (AI420-008 and AI420-066). Study AI420-007 was designed to document eradication by pathogens isolated by maxillary sinus aspiration. Study AI420-008 was designed to demonstrate the efficacy of gatifloxacin compared to clarithromycin in adults with clinically and radiologically documented acute sinusitis. Study AI420-066 was submitted to the NDA as a clinical amendment on June 11, 1999. It was designed to demonstrate the efficacy of gatifloxacin compared to trovafloxacin in the treatment of acute, uncomplicated maxillary sinusitis. The three studies had very similar designs and conduct. Only the controlled studies will be discussed in this review. For a complete discussion of study AI420-007 please see the medical officer's review.

### **Protocol AI420-008: A RANDOMIZED DOUBLE-BLIND MULTICENTER PHASE III COMPARISON OF GATIFLOXACIN TO CLARITHROMYCIN IN THE TREATMENT OF PATIENTS WITH ACUTE MAXILLARY SINUSITIS**

### **Protocol AI420-066: A RANDOMIZED DOUBLE-BLIND MULTI-CENTER COMPARISON OF GATIFLOXACIN TO TROVAFLOXACIN IN THE TREATMENT OF SUBJECTS WITH ACUTE UNCOMPLICATED MAXILLARY SINUSITIS**

#### **1. Objectives and Study Design**

The objective of study AI420-008 and study AI420-066 was to establish clinical efficacy and safety of gatifloxacin 400 mg orally once daily for 10 days compared to an active control of clarithromycin 500 mg twice daily for 14 days or an active control of trovafloxacin, 200 mg orally once daily for 10 days in the treatment of acute, uncomplicated maxillary sinusitis. Study AI420-008 was conducted at 29 study sites in the US and Canada from September 18, 1997 to April 9, 1998. Study AI420-066 was conducted at 26 study sites in the US and enrolled patients from October 12, 1998 to January 20, 1999.

The studies were both randomized (1:1), double-blind, multi-center, two arm comparative studies. Four hundred twenty five patients were enrolled in AI420-008 and 255 patients were enrolled in AI420-066. The primary inclusion criteria were facial pain or tenderness over one or both maxillary areas along with purulent discharge from either the maxillary sinus orifice, from the nose, or present in the back of the throat, and a radiologic confirmation of the clinical diagnosis of sinusitis. Due to the lag time between enrollment and radiologic confirmation a number of patients were determined to be ineligible for the study after they were enrolled and treated with the study medication. These subjects were included in the intent-to-treat analysis and removed from the per-protocol analysis.

*Reviewer's Comment: Study AI420-008 used a dynamic randomization algorithm to assign subjects to a treatment while ensuring balance between the two treatments within center (Pocock SJ and Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-115). At the present time we do not know of any appropriate analysis that takes this randomization into account. The analyses shown in this report assume that a simple randomization technique was used. It is not known if the results reported in this review are more or less conservative due to the dynamic randomization.*

*Additional details of this issue are given in the Introduction. Note that study AI420-066 used a permuted block randomization process to balance treatment within site.*

The following notation is used to indicate study periods: first day of study drug therapy is Day 1, days on which study drug was administered are Day 1, Day 2, Day 3, etc., pre-treatment days are Day -2, Day -1, etc., and post-treatment days are Day +1, Day +2, etc.. Patients were evaluated pre-treatment, during treatment, post-treatment, and at a final follow-up visit. In study AI420-008, the clinical response was based on the signs and symptoms reported at the final follow-up visit (Test of Cure visit) conducted between Day +19 to +30, or earlier for those who discontinued. The Test of Cure visit window was extended from Day +21 to +28 to include any follow-up visit between Day +19 and Day +30. This change was made in the Analysis Plan submitted on 6/19/98; study unblinding was done on 7/30/98. In study AI420-066, the clinical response was based on the signs and symptoms reported at the post-treatment visit (Test of Cure visit) conducted between Day +7 and +14, or earlier for those who discontinued. Relapses were to be assessed between Day +21 and +28 at the final follow-up visit.

At the Test of Cure visit a clinical response of cured, failure, or unable to determine (UTD) was determined for each subject. Treatment failures could be assessed anytime after 3 days of treatment. The primary efficacy variable as defined by the sponsor was the clinical response rate at the Test of Cure visit in clinically evaluable patients. The FDA considers analyses based on the intent to treat population as co-primary. The definitions of cure, failure, and unable to determine given in the BMS study report for AI420-008 are shown here:

#### CURED

- All signs and symptoms of the acute infection were improved or resolved with the original therapy alone, without need for further antimicrobials. In addition, no new signs or symptoms of acute infection were present.

#### FAILURE

- Lack of improvement of signs and symptoms of the acute infection after at least three days of study drug therapy; or
- Improvement or resolution of signs and symptoms of the acute infection at the end-of-treatment assessment (Day +1 to Day +3) followed by the recurrence of signs and symptoms at a subsequent follow-up assessment (either the Day +7 to Day +14 visit or the Test of Cure Visit in the Day +19 to Day +30 window).

#### UNABLE TO DETERMINE

- No post-treatment evaluation of signs and symptoms was done (i.e., no Test of Cure Visit); or
- The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the principal pathogens associated with acute bacterial sinusitis, but for an infection other than sinusitis, prior to assessment at the Test of Cure Visit; or
- The patient did not receive a minimum of three days of therapy.

The definition of cured for study AI420-008 was changed in an administrative letter dated October 27, 1997 from *complete resolution* of the acute signs and symptoms to *resolution or improvement* of signs and symptoms of the acute infection. The definitions of cured, failure, and UTD are slightly different for study AI420-066. In the definition of cured the following statement is not included "In addition, no new signs or symptoms of acute infection were present." In the definition of failure for AI420-066, the second bullet is not included.

Three data sets were of interest in study AI420-008; all treated patients data set is the Intent to treat data set, eligible patients data set is a modified intent to treat data set, and clinically evaluable patients data set is the per-protocol data set. In study AI420-066, only an all treated

- patients data set and a clinically evaluable data set were defined. The exact definitions of the data sets of the study report for AI420-008 are given here:

- **All Treated Patients:** All patients who received at least one dose of study drug.
- **Eligible Patients:** All Treated Patients with a diagnosis of acute maxillary sinusitis at entry, defined as:
  - Facial pain/tenderness over one or both maxillary areas, and either
    - Purulent discharge from the maxillary sinus orifice, or
    - Purulent discharge from the nose, or
    - Purulent discharge present in the back of the throat;
  - Radiologic confirmation (by x-ray or CT scan) of the clinical diagnosis of sinusitis, consisting of evidence of at least one of the following in one or both maxillary sinuses:
    - Opacification,
    - Air/fluid level,
    - Mucosal thickening of  $\geq 5$  mm.
- **Clinically Evaluable Patients:** All Eligible Patients who:
  - Received 80 - 120% of his/her study drug (at least three days for treatment failures),
  - Received a final follow-up assessment (Test of Cure Visit within the Day +19 to Day +30 window; not applicable to treatment failures),
  - Did not receive any systemic antibacterials between the pre-treatment visit and the Test of Cure Visit.

For study AI420-066 the definition of the all treated data set is the same as that given above. The definition for the clinically evaluable data set is given here:

- **Clinically Evaluable Patients:** All Treated Patients who met the following criteria:
  - Met all inclusion criteria and none of the exclusion criteria;
  - Received sufficient course of therapy (took at least 80% of study drug, or in the case of failure, took at least the first 3 consecutive days of study drug);
  - Received a Test of Cure assessment; and
  - Received no concomitant systemic antibiotics, other than study drug, unless to treat a clinical failure.

## 2. Study Population and Baseline Demographics

### *Study AI420-008*

A total of 425 patients were enrolled in 27 study centers. Of the 425 subjects enrolled in the study, 421 patients were treated; 210 received gatifloxacin and 211 received clarithromycin. Four subjects (1 on gatifloxacin and 3 on clarithromycin) were labeled as not taking any study medication and were removed from all of the data sets. Three hundred eighty-four patients (91% of all treated patients) were considered in the eligible data set (88% for gatifloxacin and 94% for clarithromycin). Three hundred three (72%) patients were considered clinically evaluable. The percent of eligible patients that were evaluable was approximately 80% for both treatments. Table IV.1 below contains the number (percent) of patients in study populations and reasons for exclusion (from Table 8.1B BMS study report for AI420-008).

**Table IV.1                      Distribution of Patients in Study Populations and  
Reasons for Exclusion  
Protocol AI420-008**

Study Population/Reason Excluded	Number (%) of Patients		
	Gatifloxacin	Clarithromycin	Total
<b>All Treated</b>	<b>210 (100)</b>	<b>211 (100)</b>	<b>421 (100)</b>
<b>Eligible</b>	<b>185 (88)</b>	<b>199 (94)</b>	<b>384 (91)</b>
<b>Ineligible</b>	<b>25 (12)</b>	<b>12 (6)</b>	<b>37 (9)</b>
<u>Reason Ineligible:</u>			
No Radiographic Documentation of Sinusitis	9 (4)	7 (3)	16 (4)
Missing Required Symptom(s) at Entry	9 (4)	1 (<1)	10 (2)
Chronic Sinusitis Rather Than Acute	5 (2)	4 (2)	9 (2)
Other	2 (1)	0	2 (<1)
<b>Clinically Evaluable</b>	<b>146 (70)</b>	<b>157 (74)</b>	<b>303 (72)</b>
<b>Unevaluable</b>	<b>65 (31)</b>	<b>57 (27)</b>	<b>118 (28)</b>
<u>Reason Unevaluable:</u>			
Ineligible	25 (12)	12 (6)	37 (9)
Post-treatment Follow-up Outside Window	16 (8)	11 (5)	27 (6)
Did Not Receive Minimum of 80% of Intended Study Drug Therapy (Excluding Failures)	9 (4)	16 (8)	25 (6)
No Test of Cure Visit	11 (5)	9 (4)	20 (5)
Other Systemic Antibiotic Received Prior to Post-treatment Follow-up	3 (1)	4 (2)	7 (2)
Other	0	2 (1)	2 (<1)

*Reviewer's Comments: The difference in percent eligible between treatments was marginally statistically significant ( $p=0.053$  using the test of equal proportions based on an exact method). Note that since eligibility is not based on treatment effects or even follow-up, this difference should not be of concern.*

*Note that subjects contained in the last 4 categories of 'Reason Unevaluable' were given the clinical response of 'unable to determine'. These subjects are counted as failures in the analysis of all treated and clinically eligible patients.*

**Study AI420-066**

A total of 255 patients were enrolled in 25 study centers. One hundred twenty four were randomized to gatifloxacin and 131 were randomized to trovafloxacin. Of the 255 subjects enrolled in the study, 253 patients were treated; 122 received gatifloxacin and 131 received clarithromycin. Two hundred twenty eight (90%) patients were considered clinically evaluable. Table IV.2 below contains the number (percent) of patients in study populations and reasons for exclusion (from Table 8.1B BMS study report for AI420-066).

**Table IV.2**                      **Distribution of Patients in Study Populations and Reasons for Exclusion**  
**Protocol AI420-066**

Study Population	Number (%) of Patients		
	Gatifloxacin	Trovafloxacin	Total
All Treated	122	131	253
Clinically Evaluable	113 (93)	115 (88)	228 (90)
Unevaluable	9 (7)	16 (12)	25 (10)
Reason Unevaluable			
No Test of Cure Visit	1 (<1)	2 (2)	3 (1)
Other Antibiotics Received	4 (3)	3 (2)	7 (3)
Insufficient Treatment	4 (3)	10 (8)	14 (6)
Other	-	1 (<1)	1 (<1)

*Reviewer's Comments:* The trovafloxacin patient in study AI420-066 listed as "other" should have been assessed an evaluable treatment failure. One gatifloxacin patient who was labeled as not taking any study medication should have been included in the all treated patients group and labeled unable to determine. These errors were noticed after the database was locked. The sponsor used the locked database in their analyses. Note that the evaluability rate is much higher in this study than in AI420-008 (90% vs. 72%).

*All subjects who were listed as unevaluable had a clinical response of 'unable to determine.' In the all treated patients analysis, these subjects are counted as failures.*

There were not large differences in the demographic characteristics gender, race, age and weight between the two treatment groups in the two studies. In study AI420-008, 63% were female, 90% were White, 6% Black, and 3% Hispanic. The mean age was 42 years with a range of 18 to 80 years and the mean weight was 80 kg with a range of 43 to 181 kg. In study AI420-066, 66% were female, 80% were White, 6% were Black, and 9% were Hispanic. The mean age was 42 years with a range of 18 to 75 years and the mean weight was 80 kg with a range of 43 to 163 kg. There were no large differences between treatment in recorded medical history, use of antimicrobial medications, or prognostic values in the two studies. The primary pre-treatment signs and symptoms of acute maxillary sinusitis had similar percentages of subjects affected between the two treatments in the two studies.

### 3. Applicant's Analyses and Results

It was stated in the protocol for study AI420-008 that gatifloxacin will be considered no worse than clarithromycin if the 95% confidence interval around the difference in cure rates did not extend beyond 15% in favor of clarithromycin, given that the observed cure rate for clarithromycin was between 80% and 89%. BMS stated in the study report that since the observed cure rate was 76%, equivalence would be determined if the lower bound did not extend beyond 20% in favor of clarithromycin.

*Reviewer's Comment:* Note that in line with the recent July 1998 Anti-Infective Advisory Committee meeting, we will consider the limit of equivalence to be independent of observed response. Since 15% was discussed in the protocol and agreed upon by the FDA, we will use 15% in determining equivalence in this study, rather than 20%. We will also use a 15% limit for study AI420-066.

*Study AI420-008*

Table IV.3 reports the study results for the all treated patients (AT), eligible (Elig) and clinically evaluable (Eval) data sets. The cure rates for clarithromycin were slightly higher than for gatifloxacin in all three data sets. The confidence intervals for the all treated patients and eligible data sets were within the 15% limit. However, the clinically evaluable data set had a lower confidence limit of -15.2. All of the confidence intervals were constructed using an exact method in StatXact.

**Table IV.3 BMS study results AI420-008**

Clinical Response	Number (%) of Patients								
	Gatifloxacin			Clarithromycin			Total		
	AT n = 210	Elig n = 185	Eval n = 146	AT n = 211	Elig n = 199	Eval n = 157	AT n = 421	Elig n = 384	Eval n = 303
Cured <sup>a</sup>	131 (62)	119 (64)	105 (72)	132 (63)	129 (65)	119 (76)	263 (62)	248 (65)	224 (74)
Failure	46 (22)	43 (23)	41 (28)	43 (20)	39 (20)	38 (24)	89 (21)	82 (21)	79 (26)
Unable to Determine	33 (16)	23 (12)	N/A	36 (17)	31 (16)	N/A	69 (16)	54 (14)	N/A

<sup>a</sup> 95% Confidence interval for the difference in Cure rate: AT (-10.0, 9.6)  
Elig (-10.9, 9.4)  
Eval (-15.2, 6.7)

*Study AI420-066*

Table IV.4 reports the study results for the all treated patients (AT) and clinically evaluable (Eval) data sets. The cure rates for trovafloxacin were slightly lower than for gatifloxacin in both data sets. The confidence intervals for both data sets were within the -15% limit. All of the confidence intervals were constructed using an exact method in StatXact.

**Table IV.4 BMS study results AI420-066**

Clinical Response	Number (%) of Patients					
	Gatifloxacin		Trovafloxacin		Total	
	AT n = 122	Eval n = 113	AT n = 131	Eval n = 115	AT n = 253	Eval n = 228
Cured <sup>a</sup>	99 (81)	99 (88)	100 (76)	100 (87)	199 (79)	199 (87)
Failure	14 (11)	14 (12)	15 (11)	15 (13)	29 (11)	29 (13)
Unable to Determine	9 (7)	N/A	16 (12)	N/A	25 (10)	N/A

<sup>a</sup> 95% Confidence interval for the difference in Cure rate: AT (-6.6, 16.7)  
Eval (-9.6, 12.2)

Table IV.5 (from table 10.1.1.2 of BMS study reports) contains the cure rates by prognostic factors for the evaluable patients. In study AI420-008, patients with a history of sinusitis, prior sinus surgery or allergic rhinitis had lower response rates than those who did not. The largest difference in cure rates between gatifloxacin and clarithromycin were in subjects without a history of sinusitis (86% gatifloxacin and 96% clarithromycin). In study AI420-066, both gatifloxacin and trovafloxacin had a slightly higher cure rate in subjects with < 3 prior episodes than in those with ≥ 3. Gatifloxacin also did better in subjects without prior sinus surgery, allergic rhinitis, and bilateral infection, and in subjects with a history of sinusitis. The

trovafloxacin arm obtained slightly higher cure rates for subjects with prior sinus surgery, allergic rhinitis, and bilateral infection, and in subjects without a history of sinusitis.

**Table IV.5 Clinical Cure Rate by Prognostic Factor, Clinically Evaluable Patients Protocol AI420-008 and AI420-066**

Prognostic Factor	Number Cured/Evaluable Patients (%)			
	Study AI420-008		Study AI420-066	
	Gatifloxacin N = 210	Clarithromycin N = 211	Gatifloxacin N = 113	Trovafloxacin N = 115
<u>History of Sinusitis</u>				
Yes	86/124 (69)	97/134 (72)	82/92 (89)	82/95 (86)
No	19/22 (86)	22/23 (96)	17/21 (81)	18/20 (90)
<u>Number of Sinusitis Episodes in Past 12 Months</u>				
<3	81/112 (72)	96/122 (79)	64/71 (90)	71/80 (89)
≥3	24/34 (71)	23/35 (66)	19/22 (86)	11/15 (73)
Unknown	-	-	16/20 (80)	18/20 (90)
<u>Prior Sinus Surgery</u>				
Yes	9/17 (53)	8/15 (53)	11/21 (79)	8/11 (89)
No	96/129 (74)	111/142 (78)	88/99 (89)	92/106 (87)
<u>Allergic Rhinitis</u>				
Yes	61/94 (65)	72/98 (73)	70/83 (89)	70/79 (89)
No	44/52 (85)	47/59 (80)	29/30 (97)	30/36 (83)
<u>Bilateral Infection</u>				
Yes	54/76 (71)	68/88 (77)	48/59 (81)	53/57 (93)
No	51/70 (73)	51/69 (74)	51/54 (94)	47/58 (81)

In study AI420-066, subjects were evaluated for relapse at the final follow-up visit between Day +21 and +28. Of the 199 evaluable cured subjects, 186 (93%) did not have a relapse, 4 (2%) were not contacted, and 9 (5%) had a relapse. There were 4 relapses on gatifloxacin and 5 on trovafloxacin. Including the relapses as failures and removing the 4 subjects who were not contacted, the cure rate for gatifloxacin was 84% and for trovafloxacin was 82%. The 95% confidence interval on the difference was (-10.1, 13.5). This interval is within the -15% limit.

*Reviewer's Comment: If the subjects who were not contacted were assumed to be relapses, the 95% confidence interval would be (-12.4, 11.5).*

In study AI420-066, there were more subjects on the gatifloxacin arm (11%) with new infections than on the trovafloxacin arm (5%). Respiratory tract infections and vaginal yeast infections were the most commonly occurring infection.

#### 4. Reviewer's Additional Analyses

*Reviewer's Comment: The analyses given in this section used the FDA defined data set, unless stated otherwise. For study AI420-008, the data set differs from the BMS defined data set in that the medical officer determined 3 subjects who were labeled as cures to be failures based on the lack of improvement of all the signs and symptoms of acute infection. Subject 005-288 who was assigned to gatifloxacin had an evaluation of worse for 'tenderness sinus' at the last visit.*

Subject 018-123 who was assigned gatifloxacin had evaluations of worse for 'pain and tenderness sinus' and 'pressure face' at the last visit. Subject 029-193 who was assigned clarithromycin had an evaluation of same for 'pain dental' at the last visit.

For study AI420-066, the FDA data set differs from the BMS defined data set in that the medical officer determined 10 subjects to be unevaluable who BMS determined to be evaluable and 2 subjects to be failures who were labeled as cures by BMS. Eight of the subjects changed to unevaluable lacked nasal purulence and 2 were cures who had a TOC visit prior to day +7. The two subjects who were changed to failure were subject 002-347 who had 'pressure' worse and subject 007-382 who had 'sinus pain' worse at the test of cure visit. Also changed in this data set are the two subjects who were miss-labeled in the sponsor's data set. One trovafloxacin patient who was labeled at unable to determine should have been assessed an evaluable treatment failure and one gatifloxacin patient who was labeled as not taking any study medication should have been included in the all treated patients group and labeled unable to determine.

Table IV.6 gives the results of the primary analyses using the FDA data set for study AI420-008. The confidence intervals for the all treated and eligible data sets were within the 15% limit. However, the clinically evaluable data set had a lower confidence limit of -16.6. All of the confidence intervals were constructed using the exact method in StatXact.

**Table IV.6 Results using FDA data set  
Protocol AI420-008**

	Number (%) of Patients								
	Gatifloxacin			Clarithromycin			Total		
	AT n = 210	Elig n = 185	Eval n = 146	AT n = 211	Elig n = 199	Eval n = 157	AT n = 421	Elig n = 384	Eval n = 303
Cured <sup>a</sup>	129 (61)	117 (63)	103 (71)	131 (62)	128 (64)	119 (76)	260 (62)	245 (64)	222 (73)
Failure	48 (23)	45 (24)	43 (29)	44 (21)	40 (20)	38 (24)	92 (22)	85 (22)	81 (27)
Unable to Determine	33 (16)	23 (12)	N/A	36 (17)	31 (16)	N/A	69 (16)	54 (14)	N/A

<sup>a</sup> 95% Confidence interval for the difference in Cure rate: AT (-10.5, 9.1)  
Elig (-11.6, 8.9)  
Eval (-16.6, 5.5)

Table IV.7 gives the results of the primary analyses using the FDA data set for study AI420-066. The confidence intervals for both the all treated and evaluable data sets were well within the 15% limit. The confidence intervals were constructed using the exact method in StatXact.

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ON ORIGINAL**

**Table IV.7 Results using FDA data set  
Protocol AI420-066**

	Number (%) of Patients					
	Gatifloxacin		Trovafloracin		Total	
	AT n = 123	Eval n = 107	AT n = 131	Eval n = 112	AT n = 254	Eval n = 219
Clinical Response						
Cured <sup>a</sup>	99 (80)	94 (88)	98 (75)	94 (84)	197 (78)	188 (86)
Failure	14 (11)	13 (12)	18 (14)	18 (16)	32 (13)	31 (14)
Unable to Determine	10 (8)	N/A	15 (11)	N/A	25 (10)	N/A

<sup>a</sup> 95% Confidence interval for the difference in Cure rate: AT (-5.8, 17.7)  
Eval (-7.0, 15.8)

Covariate Analyses

Analyses by race and gender were also conducted. No large treatment differences were seen either within or between treatments by gender or race in these two studies.

Missing Data Analyses

In the sponsor's analyses, missing data (unable to determines) were treated as failures. Since this is an equivalence trial this method of "imputing" missing values may not be conservative. The true difference may be diluted by a large number of missing values. To examine the robustness of the conclusions with regard to the missing data, a very conservative analysis was conducted. The analysis considered all missing data on gatifloxacin as treatment failures and all missing data on the controls as cures. The 95% confidence intervals calculated using an exact method are given here.

Missing Data Analysis	AI420-008	AI420-066
All Treated Patients	(-27.0%, -8.4%)	(-17.1%, 4.7%)
Clinically Eligible	(-26.6%, -7.1%)	N/A

Though none of these confidence intervals fall within the bounds of -15%, it does not mean that gatifloxacin is not equivalent to the controls. However, it does signify that the results are not robust enough for this extreme method of imputation. The confidence intervals for study AI420-008 are quite wide due to the large percentage of missing data in this study. For the all treated data set, 16% of the patients had missing data versus 10% in study AI420-066.

Bv Center Analyses

There were no centers unduly weighting the results. The large centers showed treatment effects most similar to the mean of all the treatment effects. Mantel-Haenszel confidence intervals with continuity correction were constructed to stratify by center. The results of these analyses are shown in the table below. Note that none of the confidence intervals extend past the limit of -15%.

Bv Center Analysis	AI420-008*	AI420-066
All Treated Patients	(-9.2%, 8.5%)	(-5.5%, 14.8%)
Clinically Eligible	(-10.3%, 8.1%)	N/A
Clinically Evaluable	(-13.7%, 5.4%)	(-6.7%, 7.3%)

## 5. Safety

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

There were a total of 263 patients in study AI420-008 and 199 patients in study AI420-066 who experienced one or more adverse events. In study -008, 122 were on gatifloxacin (58% of the gatifloxacin arm) and 141 were on clarithromycin (67%). In study -066, 93 were on gatifloxacin (76% of the gatifloxacin arm) and 106 were on trovafloxacin (81%). A total of 170 subjects in study -008 (75 on gatifloxacin and 95 on clarithromycin) and 151 subjects in study -066 (65 on gatifloxacin and 86 on trovafloxacin) were thought to have experienced a drug related adverse event. The most common were rhinitis, nausea, dizziness, insomnia, headache, pain and diarrhea. Most adverse events were equally distributed between the two treatments, except vaginitis and taste perversion in study -008 and vaginitis and dizziness in study -066. In study AI420-008, vaginitis was experienced more frequently in gatifloxacin treated females than clarithromycin treated females (9% vs. 1%,  $p=0.029$ ) and taste perversion was experienced more frequently in clarithromycin treatment group (3% vs. 17%,  $p=0.002$ ). In study AI420-066, vaginitis was experienced more frequently in gatifloxacin treated females than trovafloxacin treated females (13% vs. 4%,  $p=0.098$ ) and dizziness was experienced more frequently in trovafloxacin treatment group (29%, vs. 56%,  $p=0.002$ ).

In study AI420-008, there were severe adverse events in 11 (5%) of the gatifloxacin patients and in 14 (7%) of the clarithromycin patients. Two of the gatifloxacin and 7 of the clarithromycin patients discontinued study medication due to the severe adverse event. There was only one very severe adverse event. It was experienced by a clarithromycin patient, but did not lead to discontinuation of study drug. There were 3 serious adverse events (1 on gatifloxacin and 2 on clarithromycin). The gatifloxacin patient had a cerebrovascular accident and the clarithromycin patients had chest pain and pneumonia. However, none were thought to be study drug related.

In study AI420-066, there were severe adverse events in 5 (4%) of the gatifloxacin patients and in 5 (4%) of the trovafloxacin patients. There were no very severe adverse events. There were 2 serious adverse events (1 on gatifloxacin and 1 on trovafloxacin). The gatifloxacin patient had an exacerbation of her underlying bipolar disorder and the trovafloxacin patient was hospitalized for treatment of a COPD exacerbation. However, neither was thought to be study drug related.

In study AI420-008, 10 (5%) of the gatifloxacin patients and 18 (9%) of the clarithromycin patients discontinued study drug due to adverse events. The primary reasons for discontinuations were gastrointestinal problems, such as, nausea, vomiting, abdominal pain, and diarrhea. In study AI420-066, 8 (7%) of the gatifloxacin patients and 16 (12%) of the trovafloxacin patients discontinued study drug due to adverse events. The primary reasons for discontinuations were dizziness, nausea, and headache.

## 6. Statistical Reviewer's Overall Assessment and Conclusion

In study AI420-066, gatifloxacin was shown to be equivalent to trovafloxacin in all populations considered. In study AI420-008, gatifloxacin was shown to be equivalent to clarithromycin in the all treated patients and the clinically eligible populations, but not in the clinically evaluable population. The medical reviewer will have to determine if this can be considered adequate for evidence of approval.

## **V. CONCLUSIONS**

**(Which May Be Conveyed to the Applicant)**

The applicant submitted seven controlled studies conducted in support of community-acquired pneumonia (AI420-002, AI420-037, and AI420-038), acute exacerbation of chronic bronchitis (AI420-001, AI420-020), and acute sinusitis (AI420-008, AI420-066).

### **Community-Acquired Pneumonia**

The clinical response for gatifloxacin was slightly lower than for clarithromycin and levofloxacin and slightly higher than for ceftriaxone. Gatifloxacin was shown to be equivalent to the controls in all the populations considered. These results seem fairly robust and suggest that gatifloxacin is similar to the three controls in terms of efficacy.

### **Acute Exacerbation of Chronic Bronchitis**

The clinical response for gatifloxacin was slightly lower than for levofloxacin and slightly higher than for cefuroxime axetil. The sponsor's confidence intervals for the all treated patients and the clinically evaluable data sets are just within the limit for equivalence for study AI420-001 and well within the limit for AI420-020. There were differences seen in cure rate for smokers and nonsmokers. Nonsmokers on gatifloxacin and cefuroxime axetil had lower cure rates than smokers. However despite the differences, the results for smokers are quite robust and show equivalence between the two treatments in both studies. The results for non-smokers are less robust; equivalence is shown in study -020 but not in -001. Note that these studies were not powered to detect equivalence in these subgroups.

Overall, in both study AI420-001 and -020 gatifloxacin was shown to be equivalent to the controls in both the all treated and the clinically evaluable data sets. These results seem fairly robust and suggest that gatifloxacin is similar to the two controls in terms of efficacy.

### **Acute Sinusitis**

In study AI420-066, gatifloxacin was shown to be equivalent to trovafloxacin in all populations considered. In study AI420-008, gatifloxacin was shown to be equivalent to clarithromycin in the all treated patients and the clinically eligible populations, but not in the clinically evaluable population. The medical reviewer will have to determine if this can be considered adequate for evidence of approval.

**APPEARS THIS WAY  
ON ORIGINAL**

**RECOMMENDED REGULATORY ACTION:**

**From a statistical perspective, the data provided by the sponsor support the approval of gatifloxacin for the indications of community-acquired pneumonia and acute exacerbation of chronic bronchitis. The results regarding equivalence for the indication of acute sinusitis were more ambiguous. As a result the reviewing medical officer will have to determine whether gatifloxacin should be considered safe and efficacious for this indication.**

**/S/** 11/2/99  
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cc:  
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HFD-590  
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HFD-725/Dr. Higgins  
HFD-344/Dr. Thomas  
This review contains 45 pages.