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RESEARCH**

APPLICATION NUMBER:

21-061/SE2-007

21-062/SE2-008

MEDICAL REVIEW

Medical Officer Review of NDA 21-061/S-007 and NDA 21-062/S-008: Gatifloxacin (Tequin®) for the FIVE day treatment of Acute Exacerbations of Chronic Bronchitis

Date Submitted: 21 December 2000, 2 January 2001
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Date Completed: 01 October 2001

Reviewer: Rosemary Johann-Liang, M.D.

Applicant: Bristol-Myers Squibb Company
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Drug: Proprietary name - Tequin
Generic name - Gatifloxacin
Chemical name - (+)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate

Drug Class: 8-methoxyfluoroquinolone antibacterial

Route of administration: Oral Tablets, 200 mg and 400 mg
Intravenous Injection, 200 and 400 mg

Related NDA: 21-061, 21-062

THE EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

Gatifloxacin (Tequin®) is an 8-methoxy fluoroquinolone that is currently approved for a 7-10 day course treatment of acute exacerbation of chronic bronchitis and multiple other indications. In this current supplemental NDA, the applicant (Bristol-Myers Squibb Company) is seeking approval for 5-day duration of therapy for the treatment of acute exacerbation of chronic bronchitis. The dose proposed is 400 mg once a day, and the age group is 18 years and above inclusive.

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

Several labeling issues need to be addressed.

With this action

- 1) The applicant proposes to withdraw the 7-10 day duration stated in the current package insert and replace with 5-days duration for the AECB indication. *This is agreeable.*
- 2) Several re-arrangement changes are proposed under the safety section with the re-tabulated data of "over 5000 patients" treated in clinical trials from "over 4000 patients" as stated in the current insert. *These wording and percentage changes are acceptable.*

B. Other Comments

The applicant concluded that "the studies included in this application demonstrate the efficacy and safety of a five day course of gatifloxacin in the treatment of acute exacerbation of chronic bronchitis, and establish comparability to two different comparator regimens: ten days of

clarithromycin and five days of azithromycin". Upon review of all the data presented, this reviewer agrees that the above conclusions are valid based upon the agreements between the applicant and FDA at the time of trial initiation and the requirements used in the original AECB indication approval. There were several issues with this application that are worthy of note, but did not undermine the validity of the current application.

- 1) Invalidation of data from study 064 sites 23 and 24 after the original application submission caused re-analysis of the data without these sites. Overall conclusions of non-inferiority remained same without the data from sites 23 and 24.
- 2) Modification in the inclusion criteria for this AECB indication should be considered for future applications in light of increasing antimicrobial resistance and inappropriate antimicrobial use for viral syndromes. This application demonstrates the limitations of the current inclusion criteria to study the indication of AECB. The inclusion criteria for these studies utilized the Anthonisen classification on all patients with history of chronic cough. In the Anthonisen¹ study however, the use of this classification was limited to patients with COPD. Thus, the population of subjects in the applicant's studies encompassed 18 year old smokers not on any chronic medications having smoke-related cough, to 85 year old medically fragile chronic obstructive pulmonary disease patients routinely treated with oxygen therapy and respiratory medications. It is the latter type of patient developing an acute bacterial respiratory infection who would most likely benefit from broad-spectrum antimicrobial therapy. In future studies of this indication, modified inclusion criteria to target the true COPD population² is warranted.
- 3) As in the original Tequin® NDA for AECB, smokers enrolled in these trials had better clinical responses than non-smokers did. In order to understand this unusual phenomenon, the applicant was asked by this reviewer to submit tabulations of patient demography by smoking status. Review of this material showed that significantly more smokers (currently smoking at the time of trial enrollment) were younger and potentially less sick than those patients who were current non-smokers, thus explaining the poorer response by the non-smokers. This analysis further supports the conclusion that more rigorously defined population and/or trial design need to be formulated for this AECB indication for future studies.

II. Summary of Clinical Findings

Gatifloxacin (Tequin) is currently approved for the treatment of AECB. The approved treatment regimen is 400 mg (oral or intravenous) given once daily for 7-10 days. In these supplemental New Drug Applications (21-061/S-007 and 21-062/S-008), the applicant has submitted two controlled clinical trials, studies 064 and 065, to support reducing the duration of treatment for AECB to 5 days. Results from the two pivotal studies are summarized below.

Study 064: Double-blind, randomized 3 arm trial, 1:1:1 in 35 US sites. Total enrolled = 532 patients (197 patients from sites 23 and 24 excluded in analysis due to DSI investigation)
Mean age 53 years; 86% White; 83% Type I exacerbation; 1° population: Clinically Evaluable Pts

	5 day gatifloxacin (400 mg QD)	7 day gatifloxacin (400 mg QD)	10 day clarithromycin (500 mg BID)
All Enrolled (+23/24)	N=175	N=176	N=181
Enrolled (-23/24) Treated	N=110 N=109	N=114 N=113	N=111 N=108
Clinically Eval	97/109 (89%)	102/113 (90%)	101/108 (94%)
Microbiol Eval	43/109 (39%)	43/113 (38%)	41/108 (38%)
Outcome (-23/24) Clinically Eval*	86/97 (89%)	86/102 (84%)	86/101 (85%)
Microbiol Eval	N=51 total pathogens	N=49 total pathogens	N=42 total pathogens
Eradication (-23/24)	Total = 49/51 (96%)	Total = 44/49 (90%)	Total = 40/42 (95%)
<i>H. influenzae</i>	12/12	12/13	8/8
<i>S. pneumoniae</i>	12/13	5/5	6/6
<i>M. catarrhalis</i>	11/11	8/10	11/11
<i>H. parainfluenzae</i>	5/5	5/6	2/4
<i>S. aureus</i>	9/10	14/15	13/13

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

Study 065: Double-blind, randomized 3 arm trial, 1:1 in 20 US sites. Total enrolled = 296
Mean age 52 years; 80% White; All Type I exacerbation; 1° population: Clinically Evaluable Pts

	5 day gatifloxacin (400 mg QD)	5 day azithromycin (500 mg day 1; 250 mg days 2-5 QD)
All Enrolled	N=147	N=149
Treated	N=147	N=147
Clinically Eval	127/147 (86%)	125/147 (85%)
Microbiol Eval	73/147 (50%)	74/147 (50%)
Outcome (-23/24) Clinically Eval*	104/127 (82%)	92/125 (74%)
Microbiol Eval	N=88 total pathogens	N=87 total pathogens
Eradication (-23/24)	Total = 75/88 (85%)	Total = 69/83 (83%)
<i>H. influenzae</i>	11/12	15/18
<i>S. pneumoniae</i>	6/7	8/9
<i>M. catarrhalis</i>	24/26	14/16
<i>H. parainfluenzae</i>	18/22	13/18
<i>S. aureus</i>	16/19	19/22

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

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

Eight hundred and twenty-eight patients totaled the safety database for these supplements and included the patients enrolled into sites 23 and 24 of the 064 study. Forty-two percent (n=208/496) of the gatifloxacin-treated patients and 44% (n=143/325) of comparator-treated patients reported at least one adverse event. Drug-related adverse events were seen in 25% of (n=124/496) gatifloxacin-treated patients and 22% (n=70/325) of comparator-treated patients. Pooled drug-related adverse rate across the two studies for 5-day gatifloxacin treatment arm was 23% (n=75/321) whereas for 7-day gatifloxacin arm, the rate was 28% (n=49/175). The most common events among gatifloxacin-treated patients were diarrhea, nausea, and dry mouth, while diarrhea, taste perversion, and nausea were most frequently cited among comparator-treated patients. There was no evidence that gender or race influenced the incidence of adverse events; patients \geq 65 years of age had a slightly higher incidence of adverse events. Laboratory abnormalities were uncommon, and Grade 3 or 4 severity abnormalities very rare.

Hyperglycemia was more noted in gatifloxacin-treated group than in the comparator group. For patients with normal pre-treatment laboratory values in the 065 study, Grade I hyperglycemia was noted in 4 (25%) of 16 tested patients in the gatifloxacin arm in comparison to none in the azithromycin arm. In total, eight gatifloxacin-treated patients (2%) and eight comparator-treated patients (2%) discontinued study therapy because of adverse events, usually either respiratory symptoms related to the underlying infection or gastrointestinal intolerance.

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

This is reasonable since AECB is not an illness of young people. Tequin is currently labeled as Pregnancy category C. Pregnant or nursing women was excluded from these AECB studies, which was appropriate. Patients with immune, hepatic, and renal insufficiency were excluded in these AECB studies as well. Exclusion of these patients makes it difficult to predict safety and efficacy for AECB treatment in these population groups.

¹Antonisen NR, Manfreda J, Warren CPW et al. Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease. *Ann Intern Med* 1987;106:196-204

²Snow V, Lascher S, Mottur-Pilson C, et al. Evidence Base for Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease. Position Paper. *Ann Intern Med* 2001; 134: 595-599

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INTEGRATED REVIEW

**sNDA 21-061 S-007 and 21-062 S-008
TEQUIN™ Tablets (gatifloxacin) and TEQUIN™ I.V. (gatifloxacin)**

Indication: Acute exacerbation of chronic bronchitis (5 day duration)

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I. Introduction and Background

A. Drug Specifics and Indication

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

B. Armamentarium for Indication

Numerous antibiotics are approved for AECB indication (see below Table 1 in alphabetical order). Most drugs are to be given for a 7 to 14 day course for this indication. Three drugs have been approved for a 5-day duration therapy and they are designated with *.

Table 1: Current Armamentarium for “Acute Exacerbation of Chronic Bronchitis” Indication

Brand (Generic)Name	Company	Organisms listed in label	Dose and Route	Duration
Avelox (Moxifloxacin)	Bayer	<i>S.pneumoniae</i> , <i>H. influenzae</i> , <i>H. parainfluenzae</i> , <i>S. aureus</i> , <i>M. catarrhalis</i>	400 mg PO QD	5 days*
Bactrim (Timethoprim-Sulfamethaxazole)	Hoffman Roche	<i>S. pneumoniae</i> , <i>H. influenzae</i>	160 mg PO Q12H	14 days
Biaxin (Clarithromycin)	Abbott	<i>S.pneumoniae</i> , <i>M. catarrhalis</i> <i>H. influenzae</i> ,	250 mg PO Q12H	7-14 days
			500 mg PO Q12H	7-14 days
Ceclor CD (Cefaclor)	Dura	<i>S.pneumoniae</i> , <i>M. catarrhalis</i> <i>H. influenzae</i> (non-beta-lactamase producing only)**	500 mg PO Q12H	7 days (16 and older)
Cedex (Ceftibuten)	DJ Pharma	<i>S.pneumoniae</i> , <i>M. catarrhalis</i> <i>H. influenzae</i>	400 mg PO QD	10 days (12 and older)
Ceftin (Cefuroxime axetil)	Glaxo Wellcome	<i>S.pneumoniae</i> , <i>H. parainfluenzae</i> (non-beta-lactamase producing only) <i>H. influenzae</i> (non-beta-lactamase producing only)	250 or 500 mg PO BID	10 days (13 and older)
Cefzil (cefprozil)	Bristol-Myers Squibb	<i>S.pneumoniae</i> , <i>M. catarrhalis</i> <i>H. influenzae</i>	500 mg PO Q12H	10 days
Cipro (Ciprofloxacin)	Bayer	<i>M. catarrhalis</i>	500 mg PO Q12H	7-14 days

hydrochloride)				
Floxin (ofloxacin)	Ortho-McNeil	<i>S.pneumoniae</i> , <i>H. influenzae</i>	400 mg IV Q12H OR 400 mg PO Q12H	10 days
Levaquin (levofloxacin)	Ortho-McNeil	<i>S.pneumoniae</i> , <i>H. influenzae</i> , <i>H. parainfluenzae</i> , <i>S. aureus</i> , <i>M. catarrhalis</i>	500 mg IV QD OR 500 mg PO QD	7 days
Lorabid (loracarbef)	Monarch	<i>S.pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i>	400 mg PO Q12H	7 days
Maxaquin (lomefloxacin)	Unimed	<i>H. influenzae</i> , <i>M. catarrhalis</i>	400 mg PO QD	10 days
Omnicef (cefdinir)	Abbott	<i>S.pneumoniae</i> , <i>H. influenzae</i> , <i>H. parainfluenzae</i> , <i>M. catarrhalis</i>	300 mg PO Q12H OR 600 mg PO QD	5 - 10 days* 10 days (13 and older)
Septa (trimethoprim and sulfamethoxazole)	Monarch	<i>S.pneumoniae</i> , <i>H. influenzae</i>	160 mg PO Q12H (Trimethoprim)	14 days
Suprax (cefixime)	Lederle	<i>S.pneumoniae</i> , <i>H. influenzae</i>	400 mg PO QD	10 days
Tequin (gatifloxacin)	Bristol-Myers Squibb	<i>S.pneumoniae</i> , <i>H. influenzae</i> , <i>H. parainfluenzae</i> , <i>S. aureus</i> , <i>M. catarrhalis</i>	400 mg PO QD OR 400 mg IV QD	7-10 days
Vantin (cefepodoxime proxetil)	Pharmacia & Upjohn	<i>S.pneumoniae</i> , <i>M. catarrhalis</i> <i>H. influenzae</i> (non-beta-lactamase producing only)	200 mg PO Q12H	10 days
Zagam (sparfloxacin)	Bertek	<i>C. pneumoniae</i> <i>M. pneumoniae</i> <i>S.pneumoniae</i> , <i>H. influenzae</i> , <i>H. parainfluenzae</i> , <i>S. aureus</i> , <i>M. catarrhalis</i>	200 mg PO BID first day, then 200 mg PO QD	10 days
Zithromax*** (azithromycin)	Pfizer	<i>S.pneumoniae</i> , <i>M. catarrhalis</i> <i>H. influenzae</i>	500 mg PO first day, then 250 mg days 2-5	5 days*

*5 day duration therapy labeled

**unless indicated, both beta-lactamase positive and negative producing strains for *H. influenzae* and *M. catarrhalis*

***Zithromax is labeled for "acute bacterial exacerbations of chronic obstructive pulmonary disease"

C. Important Milestones in Product Development

Gatifloxacin was discovered _____ licensed development rights in the United States, Canada, Mexico, Argentina, Brazil, South Africa and Australia to Bristol-Myers Squibb Company in October 1996. INDs were filed for the oral formulation of gatifloxacin _____ on 26 November 1996 and for the intravenous formulation _____ on 23 June 1997.

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Bristol-Myers Squibb filed NDAs (#21-061, #21-062) for the oral and intravenous formulations of gatifloxacin on December 18, 1998. The NDAs comprised data from 6700 patients (4300 gatifloxacin) enrolled in Phase I, II, and III studies. On December 17, 1999, gatifloxacin was approved for six different indications: community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), acute sinusitis, uncomplicated urinary tract infections, complicated urinary tract infections (including pyelonephritis), and uncomplicated gonorrhea. The recommended treatment duration ranged from a single dose to 14 days, depending on the indication. Since its approval, [REDACTED] patients have received prescriptions for Tequin®.

Since this supplemental application was seeking to revise an already approved indication to a shorter duration of therapy, no substantial issues were encountered during the development and execution of the pivotal studies. The design and conduct of the two pivotal studies were consistent with the Infectious Diseases Society of America (IDSA) and the Food and Drug Administration (FDA) Guidelines for the evaluation of anti-infective drugs in the treatment of AECB. They were randomized, double-blind, multicenter studies designed to compare the safety and efficacy of gatifloxacin to two standard regimens. The original medical officer review for the AECB indication was written by Ziad Akl, M.D. and the gatifloxacin umbrella reviewer was Joyce Korvik, M.D., M. P. H. with Team Leader Marc Cavaille-Coll, M.D., Ph.D. The prior review stated that in line with the July 1998 Anti-infective Advisory Committee meeting, the limit of equivalence was considered independent of the observed response and 15% was discussed and agreed upon by the FDA in reference to all gatifloxacin submissions at that time. For the current supplemental NDA, the applicant also used this 15% limit of equivalence in both of their pivotal studies.

Just prior to the submission of these NDA supplements, several issues were brought to the FDA's attention. The background package from the applicant (submitted October 30, 2000) in preparation for the December 8, 2000 pre-NDA meeting listed the following proposals.

1. If the supplements are approved, the applicant wanted to withdraw the "7-10 day" treatment for AECB and replace with "5 day" regimen under the package insert section - Dosage Guidelines. (The Division agreed to this proposal.)
2. The study conducted by gatifloxacin's developer in [REDACTED] was going to be presented as "Additional Information". The applicant felt that although the [REDACTED] study was supportive of their application, full integration of data was not possible due to significant differences in the study design between the [REDACTED] study and the United States pivotal trials. (The Division agreed to this proposal. There will be no electronic or dataset submissions of the [REDACTED] study. This European study will be reviewed as supportive report only.)
3. Two investigators (Dr. C. Andrew DeAbate and Dr. C. P. Mathew, both of New Orleans, LA) who had contributed a large number of subjects (37% together) to the applicant's first pivotal study (Study A1420-064) were under scrutiny by the FDA's Office of Scientific Investigations. The applicant stated that when they learned of this problem, they performed an internal audit of the sites as well as an independent outside audit. Since the applicant was not aware of any official substantive action against these investigators at that time, the applicant wanted to include all efficacy and safety analyses from these two sites (site 23 and 24) for their submission. They did indicate that efficacy analysis excluding the two sites did not change their overall conclusion of equivalence, although the confidence intervals around the point estimates were widened. (The Division agreed to the inclusion of the data from these two sites for the December submission with the independent audit report. However, if at any point in the review, questions arise regarding these two sites, the applicant will be asked to re-do the analysis excluding the data from the two sites). Subsequently, the Division did request a reanalysis of the 064 study data without the 3 sites [see section IV(A)].

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D. Other Relevant Information

An OPDRA Postmarketing Safety Review has been recently completed by Sarah J. Singer, R.N., Safety Evaluator from the Division of Drug Risk Evaluation II to assist the review of the this application. In her review, she uses the IMS Health NPA Plus™ database to give us an idea of the utilization of Tequin®. Between January 2000 and March 2001, _____ prescriptions for oral Tequin® were filled by retail pharmacies in the United States. During the same period for inpatient facilities, more than _____ tablets and _____ of Tequin® were purchased. Worldwide, utilization is probably much less for Tequin® than in the United States. To date, the only countries aside from United States that have approved gatifloxacin are Mexico, Brazil, and Argentina. The query to the National Disease and Therapeutic Index database showed that more than 75% of gatifloxacin use was in patients 19 to 64 years of age, and most of the remainder was in patients aged 65 and over. Less than 2% of patients receiving drug were less than 18 years of age. [see Appendix 3; OPDRA consult]

E. Important Issues with Pharmacologically Related Agents

In the same OPDRA review, gatifloxacin post-marketing events were compared to the pharmacologically similar agent, moxifloxacin experience. This was due to several concerning spontaneous reported adverse events for both drugs. Numerous caveats were listed which must be considered in reporting rate comparisons (complete review: Appendix 3). Most notably, Bristol-Myers Squibb has a waiver filed to not submit individual report forms for Tequin® -associated nonserious labeled events. The company merely lists those events in their periodic reports for the drug. Bayer has not filed such a waiver for Avelox®, so presumably the total adverse events reports (AERS) counts for Tequin® would be lower than those for Avelox®, even if both drugs were suspect in the same numbers of adverse events. The emphasis in her document however, was on serious unlabeled events, for which no waivers are granted. OPDRA recommended the following adverse events to be added to a new post-marketing subsection in the label.

These supplement applications proposes to cut down on the amount of medication to be used in each individual for the same indication (i.e. 7-10 day therapy to 5-day therapy for AECB). This decrease in exposure to drug is positive for the safety profile in the individual taking that course of therapy. However, the increased convenience and compliance with this therapy regimen may increase utilization in the overall population and thus an increase post-marketing adverse event numbers could be the result.

II. Clinically Relevant Finding from other disciplines

Taken from Conclusions and Summary sections of Microbiology Review by Peter A. Dionne: (Please see full review for details): Over 60% of patients had a pre-treatment pathogen identified. Of the three key respiratory pathogens *Moraxella catarrhalis* was the most frequently identified pathogen (71 isolates, all but two of which produced β -lactamase). There were 58 isolates of *Haemophilus influenzae* (one-third produced a β -lactamase), 49 *Streptococcus pneumoniae* isolates of which 10 were penicillin-intermediate and only two were penicillin-resistant. There were also 92 *Staphylococcus aureus* isolates and 61 *Haemophilus parainfluenzae* isolates recovered pre-treatment. The overall microbiological eradication rates in the pooled arms were comparable (91% gatifloxacin, 88% comparators). For *streptococcus pneumoniae*, the comparators eradicated 14 of 15 isolates, while gatifloxacin eradicated 18 of 20. Eradication rates for *Haemophilus influenzae* and *Moraxella catarrhalis* were favorable in both treatment groups. Only three organisms (two isolates of methicillin-resistant *S. aureus* and one of *Pseudomonas putida*) were not susceptible to gatifloxacin. *No new microbiological pre-clinical information is provided in the supplement. The supplement may be approved from the microbiological viewpoint. There are no microbiological points to convey to the applicant. No changes are needed in the Microbiology subsection of the label.*

Taken from Conclusions section of Statistics Review by Nancy Silliman (Please see full review for details):

The primary efficacy endpoint in each study was the clinical cure rate at the test-of-cure visit, 5 to 18 days post-therapy. The applicant considered the results in the clinically evaluable patient population to be primary. This reviewer considers the results in eligible patients to be equally important. In both studies, efficacy rates were found to be similar among treatment groups. In study 064, the 95% confidence interval for the difference in clinical cure rates, 5-day gatifloxacin minus clarithromycin, was (-6.1%, 7.0%) in all clinically evaluable patients, and (-5.3%, 12.3%) in clinically evaluable patients excluding those enrolled by Drs. DeAbate and Mathew. In eligible patients in study 064, the 95% confidence intervals for the difference in clinical cure rates, 5-day gatifloxacin minus clarithromycin, were (-7.7%, 6.4%) (all eligible patients), and (-6.3%, 11.6%) (Eligible patients excluding those enrolled by Drs. DeAbate and Mathew). In study 065, the 95% confidence interval for the difference in cure rates, gatifloxacin minus azithromycin, was (-3.4%, 17%) in clinically evaluable patients and (-5.2%, 15.3%) in eligible patients. *From a statistical perspective, the data provided by the applicant in this submission support the approval of a 5-day course of treatment, 400 mg gatifloxacin QD, in the treatment of acute exacerbation of chronic bronchitis.*

III. Human Pharmacokinetics and Pharmacodynamics

No new pharmacokinetic and pharmacodynamic issues were raised with this supplement. The clinical data supporting this new claim (5-day duration therapy for AECB) was obtained using only the tablet formulation and this was filed to NDA #21-061. However, because the intravenous route of administration for Tequin® gives C_{max} and AUC levels equal to or greater than the oral, the submission for Tequin® intravenous (NDA #21-062) was cross-referenced to NDA #21-061.

IV. Description of Clinical Data and Sources

A. Overall Data

The organization of these sNDA followed the format described in 21 CFR 314.70, NDA Content and Format. Seven volumes were submitted with Volume 1 containing proposed label change and application summary; Volume 2 with hard-copy references; Volume 3 with environmental assessment statement for chemistry, manufacturing, and controls; Volume 4 is the clinical study report/data for the first pivotal study; Volume 5 is the clinical study report/data for the second pivotal study; Volume 6 was the supportive study from Europe; and Volume 7 contained the CD-ROM SAS Transport Files and Case Report Forms for All Patients Dying or Discontinuing Therapy Due to Adverse Events Within 30 Days of Drug Treatment.

The applicant was asked in March of 2001 to submit re-tabulations excluding the data from the two sites under investigation because the review of the independent audit was not comprehensive of all enrolled patients. A complete re-tabulation of all tables in the 064 study and integrated analysis with pertinent re-tabulated appendices were submitted for further review on May 24, 2001.

B. Table Listing the Clinical Trials

Table 2: Overview of Studies submitted

Protocol	Study Type	Dose and Duration	Number of Patients
AI420-064 (USA)	Multicenter, randomized, double-blind controlled trial	Gatifloxacin 400 mg PO qd 5 days vs Gatifloxacin 400 mg PO qd 7 days vs Clarithromycin 500 mg PO bid 10 days	532 patients enrolled *site 23 (#97) and site 24 (#100) = 37% of patients
AI420-065 (USA)	Multicenter, randomized, double-blind controlled trial	Gatifloxacin 400 mg PO qd 5 days vs Azithromycin 500 mg day 1 followed by 250 mg days 2-5 PO	296 patients enrolled
Study No. <i>Study No. KF5501/03 (Europe)</i> (Submitted as additional information only)	<i>Multicenter, multinational, randomized, double-blind controlled trial</i>	<i>Gatifloxacin 200 mg PO qd 5 days vs Gatifloxacin 400 mg PO qd 5 days vs Augmentin (500 mg Amoxicillin/ 125 mg Clavulanic Acid) PO tid 10 days</i>	<i>414 patients enrolled</i>

*PIs for these two sites under investigation

C. Postmarketing Experience

See previous sections I(D), I(E), and Appendix 3

V. Clinical Review Method

The two pivotal trials (064 and 065) were first reviewed separately. Efficacy and safety reviews were conducted for each trial separately. As mentioned above in section IV(A), data from sites 23/24 were not deemed reliable by the DSI audit, and thus for study 064, the review was conducted initially with all sites, then with sites 23/24 excluded. Appendix 1 (which describes study 064 in detail) presents the review with and without sites 23/24 in tandem. Appendix 2 presents the 065 study in detail. Data from the 2 studies were then pooled together for this integrated review. For the efficacy review, sites 23 and 24 were excluded. For the safety review, patients from sites 23 and 24 were not excluded.

The medical officer and statistician reviews from the original Tequin® AECB application were read by this reviewer to allow consistency in this supplemental NDA review. Electronically submitted datasets and case report forms, as well as hard-copy tabulated data submissions were used in the review. Trials appeared to be conducted in accordance with accepted ethical standards. A listing of all investigators and subinvestigators included financial disclosure section and the applicant made an "earnest effort" to provide financial disclosure information on all the investigators and subinvestigators. There did not appear to be any financial disclosures issues, which in the opinion of this reviewer, could cast doubt on the findings.

IV. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The applicant concluded that "the studies included in this application demonstrate the efficacy and safety of a five day course of gatifloxacin in the treatment of acute exacerbation of chronic bronchitis, and establish comparability to two different comparator regimens: ten days of clarithromycin and five days of azithromycin". Upon review of all the data presented, this reviewer agrees that the above conclusions are valid based upon the agreements between the applicant and FDA at the time of trial initiation and the requirements used in the original AECB indication approval. There were several issues with this application that are worthy of note, but did not undermine the validity of the current application.

- 1) Invalidation of data from study 064 sites 23 and 24 after the original application submission caused re-analysis of the data without these sites. Overall conclusions of non-inferiority remained same without the data from sites 23 and 24.
- 2) Modification in the inclusion criteria for this AECB indication should be considered for future applications in light of increasing antimicrobial resistance and inappropriate antimicrobial use for viral syndromes. This application demonstrates the limitations of the current inclusion criteria to study the indication of AECB. The inclusion criteria for these studies utilized the Anthonisen classification on all patients with history of chronic cough. In the Anthonisen¹ study however, the use of this classification was limited to patients with COPD. Thus, the population of subjects in the applicant's studies encompassed 18 year old smokers not on any chronic medications having smoke-related cough, to 85 year old medically fragile chronic obstructive pulmonary disease patients routinely treated with oxygen therapy and respiratory medications. It is the latter type of patient developing an acute bacterial respiratory infection who would most likely benefit from broad-spectrum antimicrobial therapy. In future studies of this indication, modified inclusion criteria to target the true COPD population² is warranted.
- 3) As in the original Tequin® NDA for AECB, smokers enrolled in these trials had better clinical responses than non-smokers did. In order to understand this unusual phenomenon, the applicant was asked by this reviewer to submit tabulations of patient demography by smoking status. Review of this material showed that significantly more smokers (currently smoking at the time of trial enrollment) were younger and potentially less sick than those patients who were current non-smokers, thus

explaining the poorer response by the non-smokers. This analysis further supports the conclusion that more rigorously defined population and/or trial design need to be formulated for this AECB indication for future studies.

¹Antonisen NR, Manfreda J, Warren CPW et al. Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease. *Ann Intern Med* 1987;106:196-204

²Snow V, Lascher S, Mottur-Pilson C, et al. Evidence Base for Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease. Position Paper. *Ann Intern Med* 2001; 134: 595-599

B. General Approach to Review of Efficacy of the Drug

The two pivotal studies (064 and 065) were reviewed in detail. Each study was reviewed separately and this analysis is attached as part of Appendix 1 (064) and Appendix 2 (065).

The efficacy datasets were analyzed via the applicant's electronic dataset submission. The evaluability criteria for clinical efficacy analysis consisted of four patient populations [See section VI (C.3) for the data set descriptions]

Individual case report forms (crfs) and narratives for patients not able to be evaluated by the 4 population datasets [see section IV(C.3)] were reviewed via electronically submitted crfs to understand and verify the reasons of ineligibility and unevaluability.

A random 10 % sample of the crfs from patients included in the above datasets was reviewed to verify the efficacy results as listed in the electronic datasets.

The efficacy datasets were verified by this reviewer with analysis in the Modified Intent To Treat (MITT) and the Modified Clinically Evaluable (MCE) populations. Criteria for MITT and MCE [See section VI (C.3) for data set descriptions] in keeping with the fact that usage of antibiotic therapy for the indication of AECB is to treat a bacterial respiratory infection. To this end, only patients with pre-treatment purulent sputum (Gramstain with >25 PMN/LPF) and a pretreatment culture with the major respiratory pathogens *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were included in this FDA MITT analysis.

C. Detailed Review of Trials by Indication

C.1 Protocol Specifics

Two randomized, double-blind, multicenter studies were designed to compare the safety and efficacy of gatifloxacin, given orally at a dose of 400 mg once daily, to a standard regimen of either clarithromycin, 500 mg BID for 10 days (Study AI420-064) or azithromycin, 500 mg on Day 1, followed by 250 mg QD for 4 days (AI420-065). Randomization to treatment was stratified by corticosteroid use at entry. In study 064, a steroid user was defined as any patient who was receiving systemic corticosteroids at time of randomization. In study 065, a steroid user was defined as any patient who was receiving either systemic, or inhaled corticosteroids at the time of randomization.

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

- 1) Eighteen years of age or older

- 2) Clinical diagnosis of acute exacerbation of chronic bronchitis, defined as:
- The presence of purulent sputum confirmed by Gram stain [>25 polymorphonuclear leukocytes (PMN) per low power field (LPF)]
 - The presence of at least two of the following signs and symptoms (Type I or II exacerbation):
 - increase cough and/or dyspnea
 - increased sputum volume
 - increased sputum purulence

**** IN STUDY 065, PATIENTS WERE REQUIRED TO HAVE ALL FOUR OF THE CARDINAL SIGNS AND SYMPTOMS: increased cough, dyspnea, sputum volume, and sputum purulence. (Type I exacerbation)****

- 3) A negative urine pregnancy test within two days prior to enrollment
 4) Written informed consent (from patient or their guardians) before any study procedure were performed

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

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

MO COMMENT: Inclusion and exclusion criteria were clearly identified prior to initiation of the study. Patients with exacerbation Type 1 and Type 2 (see below) were included in 064 study. This is different from trial 2 where only Type 1 was included. Also different from trial 2 was randomization by systemic corticosteroid use only. The exclusion of patients with AIDS, renal insufficiency, and hepatic disease makes it difficult to predict safety and efficacy in these population groups.

Although only the presence of purulent sputum (as defined by >25 PMNs/LPF) was the criteria used for inclusion in this study, the dataset GRAMSTAIN was analyzed by this reviewer to ensure that the majority of these sputum samples also had <10 epithelial cells and that this quality of the sputum was comparable across the three arms. Out of the total 2016 samples (pre-treatment samples, some patients with multiple samples) of sputum from both studies, the breakdown by the number of epithelial cells in the sputum was analyzed as follows (Table 3). Comparator group is clarithromycin group from 064 plus the azithromycin treated group from 065. The 7-day gatifloxacin treated group from study 064 is not included in this table (but can be found in Appendix 1). The two groups are comparable in the quality of the sputum samples with the majority of patients in both groups having <10 epithelial cells/LPF.

Table 3: Gramstain quality

# epithelial cells/LPF	Gatifloxacin	Comparator
<10	605	615
10-25	122	157
>25	23	14

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

- Type I: increase dyspnea, increase sputum volume and increased sputum purulence

- Type II: any two of the three symptoms of Type I
- Type III: any one of the three symptoms of Type I

In both studies, gatifloxacin was administered orally at a dose of 400 mg once daily for five days. Study 064 also included a 7-day gatifloxacin treatment arm. Also in study 064, active therapy was followed by placebo for 5 or 3 days to fill out a complete 10 day course. The active control in study 064 was clarithromycin, which was dosed 500 mg PO twice daily for ten days. In study 065, the comparator was azithromycin, administered as a single PO 500mg dose, followed by 250 mg PO daily for four days. In both studies, the study regimens were administered in a double-blind, "double-dummy" fashion in order to mask the identity and unit dose size. Medications were supplied in blister cards with enough drug for 10 (064) or 5 (065) days.

***MO COMMENT:** The comparator CLARITHROMYCIN is currently labeled in the treatment of AECB at the following doses for the different pathogens: H. influenzae -500 mg BID for 7-14 days, H. parainfluenzae -500 mg BID for 7 days, M. catarrhalis -250 mg BID for 7-14 days, and S. pneumoniae -250 mg BID for 7-14 days. Thus, the dose used in this study 064, namely 500 mg BID for 10 days was appropriate. The comparator AZITHROMYCIN is currently labeled in the treatment of AECB for H. influenzae, M. catarrhalis, and S. pneumoniae with the dose of 500 mg QD first day followed by 250 mg QD for days 2 through 5. Thus, the dose used in study 065 was appropriate.*

No doses of any other systemic antibiotics were permitted from the time of enrollment until completion of the post-treatment procedures. Other antimicrobial agents, such as antivirals and antifungals, were permitted. Adjunctive measures, such as oral or topical decongestants, antihistamines, and intranasal steroids, were permitted during and post-treatment as needed by the patient. In addition, concomitant or post-treatment non-drug therapies, such as postural drainage or oxygen were allowed. Investigators were permitted to discontinue study drug and remove patients from the study for the following reasons:

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

Patient assessments were scheduled to occur as follows:

- Pre-treatment (within 48 hours before dosing) office/clinic visit
- During treatment (Day 3 to Day 5) office/clinic visit (Study 064 ONLY)
- End of treatment (Day +1 to Day +3) telephone contact (office/clinic visit for further evaluation if not clinically improved)
- Post-treatment (Day +5 to Day +18) office/clinic visit (Test-of-Cure)
- Extended Follow-up (Day +21 to Day +28) telephone contact

The pre-treatment data were collected within the two-day period prior to the start of therapy. The characteristics which were summarized consisted of demography; medical history (including pulmonary history); signs and symptoms of AECB; sputum examination of culture results; prognostic factors including exacerbation type (by definition, all patients in 065 were to have Type I exacerbations), duration of current episode of AECB, current smoking status, history of smoking, and steroid use (systemic and/or inhaled). Exacerbation type at entry was determined according to the Anthonisen criteria: 1) Type I – increased dyspnea, increased sputum volume and increased sputum purulence 2) Type II – any two of the three symptoms of Type I 3) Type III – any one of the three symptoms of Type I.

A central laboratory performed all laboratory procedures, including cultures. All sputum specimens (>25 PMN per LPF) were plated semi-quantitatively for aerobic growth, and all potential pathogens isolated were tested for susceptibility to gatifloxacin and the comparator agent by the disk diffusion and minimum inhibitory concentration (MIC). Hematology, serum chemistry, and urinalysis tests were obtained. White blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, and microscopic urinalysis were included. A urine pregnancy test was performed on all women of childbearing potential. Positive urine pregnancy tests were confirmed with a serum-based pregnancy test.

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

C.2 Efficacy Endpoints

Clinical and bacteriologic responses were determined from data at the TOC visit occurring from Day +5 and Day +18. Treatment failures could be assessed earlier. Relapses were assessed at the final follow-up visit (Day +21 to Day +28). Investigators assigned a clinical response to each patient and a bacteriologic response to each pre-treatment pathogen. If a patient did not have a post-treatment visit, a response was derived from any available data during or post-treatment. Each patient was assigned a clinical response of Cured, Failure, or Unable to Determine with every possible attempt at either a Cure or Failure assignment. For discrepancies between the Investigators and the BMS Medical Monitor where a consensus cannot be reached, the efficacy analyses were based on the responses assigned by the Medical Monitor.

MO COMMENT: Because the studies allowed for a derivation of response from any available data during or post-treatment if a patient did not have a post-treatment visit, the discrepancies between the investigators' response assessment and the BMS Medical Monitors' response assessment were carefully reviewed. Appendix 4 of this sNDA volumes 4 and 5 gives 84 instances (total) where the Investigator's evaluation of clinical response differed from the Medical Monitors. Table 3 below compares the different reassignments by the Medical Monitor between the 5-day gatifloxacin arm and the two comparator arms (clarithromycin for 064 and azithromycin for 065) taken together. The 7-day gatifloxacin arm numbers from study 064 is not shown, but the numbers in that arm were also comparable. The numbers/categories of patients whose clinical responses were reassigned were similar across the studies and between the gatifloxacin 5-day and comparator arms.

Table 4: Discrepancies in Response Reassigned

<i>Clinical response reassigned By BMS Medical Monitor</i>	<i>Gatifloxacin 5-day arm Discrepancies (n=33)</i>	<i>Comparator arm Discrepancies (n=31)</i>
<i>From Cured to Failure</i>	<i>10 patients</i>	<i>14 patients</i>
<i>From UTD, NA, or Failure to Cured</i>	<i>14</i>	<i>11</i>
<i>From UTD, NA, or Cured to Failure</i>	<i>8</i>	<i>6</i>

The definitions used by the applicant for clinical response were as follows:

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

clinical signs and symptoms of acute infection appeared, or if present at study entry, the patient still has fever (i.e., temperature > 38°C or 100.4°F), or clinical/radiological evidence of pneumonia; or another antibiotic was required for treatment of this acute episode despite the resolution or improvement of signs and symptoms. **UNABLE TO DETERMINE:** No follow-up beyond the pre-treatment visit **RELAPSE:** Worsening or recurrence after initial improvement/resolution of the signs and symptoms related to the acute infection; or appearance of new signs and symptoms of acute respiratory infection without documentation of a new pathogen.

The definitions used by the applicant for bacteriologic response were as follows:

ERADICATED: The original pathogen was absent in the culture of a good quality (i.e., > 25 PMN/LPF) sputum specimen obtained at the TOC visit. **PRESUMED ERADICATED:** The subject was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was cured.

PERSISTED: The original pathogen was present in the culture of a good quality (i.e., > 25 PMN/LPF) sputum specimen obtained at the TOC visit. **PRESUMED PERSISTED:** The subject was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was failure.

UNABLE TO DETERMINE: The clinical response of the patient in question was designated Unable to Determine. A **by-patient bacteriologic response** was computed for each patient with at least one pathogen isolated pre-treatment. The by-patient response incorporates the bacteriologic responses for all pre-treatment sputum pathogens isolated for a patient. For example, a patient with two pre-treatment pathogens, one eradicated and one persisted, was assigned the by-patient bacteriologic response of ERAD/PERS. No distinction was made between documented and presumed responses. **PERSISTENT PATHOGENS** were tested for susceptibility to both study drugs as well as to other appropriate antibiotics. **RELAPSE** from the clinical response of Cured at the TOC visit was evaluated at the extended follow-up assessment (Day +21 to Day +28). A patient was considered to have relapsed if they were given an alternative antibiotic therapy because of signs and symptoms of an acute bronchial infections. Pathogens isolated from relapsed patients were speciated and tested for susceptibility to gatifloxacin, and other antibiotics as appropriate.

A **NEW INFECTION** was defined as the occurrence, at any time during or after study therapy of one of the following: isolation of any pathogen from a new site of infection, with associated clinical signs and symptoms or the presence of clinical signs and symptoms indicative of a new infection for which a culture would not usually be obtained (e.g., skin infection). Pathogens isolated from patients with new infections were speciated and tested for susceptibility to gatifloxacin, and other antibiotics as appropriate.

***MO COMMENT:** A theoretical quandary is this: how is "improvement" truly assessed? There are no available validated tools that assess clinical response for patients in AECB trials like this. There are no objective criteria, scoring system, pulmonary function tests pre-post, etc. in this trial. The assessment of "improved" or "same" or "worse" is all currently subjective for assessment of patients in this indication. With that perspective in mind, the clinical and bacteriologic endpoints were adequately defined prior to study initiation.*

C.3 Statistical Considerations

Data Set Descriptions (Four Study Populations of Interest)

All Treated Patients: All patients who received at least one dose of study therapy

Eligible Patients: All Treated Patients with a diagnosis of AECB at entry (purulent sputum confirmed by Gram stain examination of >25 PMN per low power field, and the presence of at least two of the signs and symptoms: increased cough and/or dyspnea, increased sputum volume, increased sputum purulence for 064 and all of the signs and symptoms for 065), and no evidence of pneumonia by chest X-ray.

Clinically Evaluable Patients: All Eligible patients who took at least 80% of study drug (with the exception of 3 days for treatment failures); had a post-treatment clinical assessment within the window for the Test of Cure Visit (or earlier 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 pre-treatment pathogen susceptible to both gatifloxacin and the comparator. Pathogens susceptible to both study drugs were considered microbiologically evaluable.

MO COMMENT: The 4 datasets correspond to the definitions for the indication of AECB in the initial gatifloxacin NDA application that was approved for 7-10 days duration. FDA clinical efficacy analysis utilized the following evaluability criteria which is in keeping with using antibiotic therapy to treat acute exacerbation of chronic bronchitis. The modified intent to treat group (MITT) and the modified clinically evaluable (MCE) groups will be analyzed to verify the efficacy results obtained by the applicant. MITT evaluable population will include all patients enrolled EXCLUDING those who

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

- 3) *had a positive chest x-ray*

MCE population will include all MITT patients EXCLUDING those who

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

Analyses of the pre-treatment characteristics and study medication usage for All Treated, Eligible, and Clinically Evaluable Patients by treatment group, were performed. Descriptive statistics were provided for the pre-treatment characteristics of interest, including gender, age, race, pre-treatment signs and symptoms, and prognostic factors. For each treatment group, pre-treatment microbiology data included the frequency of patients with single or multiple pathogens, as well as a summary of the frequency of isolation of the most common organisms. Susceptibility of pretreatment pathogens to gatifloxacin and comparators was also summarized.

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

MO COMMENT: The lower limit of confidence at -15% was agreed upon by the FDA in reference to all submitted gatifloxacin protocols at the time of the original gatifloxacin application, and was used in the original application. The Fleiss method calculates adjusted confidence limits based on "weighted average of the stratum-specific rate differences, where the inverse of the variance of estimated rate difference within the stratum was used as the weight for the corresponding stratum". Our statistician (Nancy Silliman) is in agreement with this method.

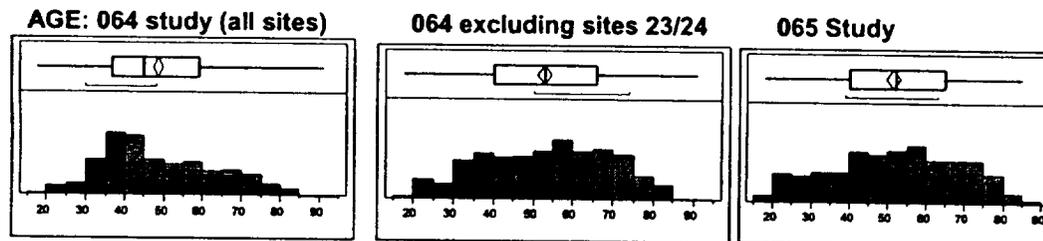
C.4 Integrated Efficacy Results

(For the purpose of this integrated efficacy evaluation, the data from 193 subjects enrolled through sites 23 and 24 will be omitted since they were deemed invalid. Please see detailed "in tandem" presentation of study 064 efficacy data which shows results including sites 23/24 data followed by results excluding those sites. Also, the comparator arm for this integrated efficacy analysis includes patients who received clarithromycin or azithromycin. This comparator arm excludes the 7-day gatifloxacin treated patients.)

Table 5: Pre-Treatment Characteristics

	No. (%) of Patients					
	5-Day Gatifloxacin			Comparator		
	064 N=109	065 N=147	Total N=256	064 N=108	065 N=147	Total N=255
Gender (%)						
Male	58 (53)	65 (44)	123 (48)	48 (44)	72 (49)	120 (47)
Female	51 (47)	82 (56)	133 (52)	60 (56)	75 (51)	135 (53)
Age (years)						
Median	51	50	51	55	54	55
Range	18-84	18-85	18-85	22-86	18-85	18-86
<65	80 (73)	110 (75)	190 (74)	77 (71)	109 (74)	186 (73)
65-74	18 (17)	21 (14)	39 (15)	24 (22)	29 (20)	53 (21)
> 75	11 (10)	16 (11)	27 (11)	7 (7)	9 (6)	16 (6)
Race						
White	98 (90)	116 (79)	214 (84)	92 (85)	120 (82)	212 (83)
Black	8 (7)	18 (12)	26 (10)	14 (13)	19 (13)	22 (13)
Hispanic	3 (3)	7 (5)	10 (4)	2 (2)	4 (3)	6 (2)
Asian	—	5 (3)	5 (2)	—	4 (3)	4 (2)
Other	—	1 (<1)	1 (<1)	—	—	—

MO COMMENT: Pre-treatment characteristics are similar between the pooled gatifloxacin arm and the comparator arm. It is notable that the range of age for the subjects is 18 to 85 years of age and that the majority (~75%) of the subjects are <65 years of age. The inclusion criteria may need to be tightened in future AECB trials to capture the patients who are truly at risk of bacterial respiratory infections exacerbating chronic pulmonary disease. I would think that very few teenagers and patients of 20-30 years would fit this picture. Of interest is the fact that the original median age (which included the patients from sites 23/24) was 46 years for the 5-day gatifloxacin arm and 45 years for the comparator. It appears that the patients who were excluded were the younger patients, who are most unlikely to have AECB, but a viral or smoking-related bronchitis.



All patients presented with symptoms of coughing and sputum production. All but 4 patients also presented with purulent sputum. Due to the different entry criteria, 87-90% of patients in 064 study entered with the symptom of dyspnea where as all but 5 patients in the 065 study presented with this symptom. Other presenting symptoms ranging from 66% of the patients down to 26% of the patients included chest tightness, sinus congestion, malaise, chest pain and chills. At presentation, the majority of patients (52% for 5-day gatifloxacin arm and 49% for comparator arm) had 1-7 day duration of the current episode. Twenty-four % of the patients in the 5-day gatifloxacin arm had 8-14 days duration verses 28% of the comparator patients. Similarly, 22% had >14 days duration in the 5-day gatifloxacin arm verses 20% in the comparator arm. The numbers for two prognostic factors are shown below to illustrate the change in values when Dr. DeAbate and Dr. Mathews sites were removed from analysis.

Table 6: Prognostic Factors: Change in numbers with or without sites 23/24 in 064 study

	No. (%) of Patients					
	5-Day Gatifloxacin			Comparator		
	064 with 23/24 N=174	064 without 23/24 N=109	065 N=147	064 with 23/24 N=178	064 without 23/24 N=108	065 N=147
Inhaled or systemic steroids use						
YES	25 (14)	25 (23)	68 (27)	36 (20)	35 (32)	44 (30)
NO	149 (86)	84 (77)	188 (73)	142 (80)	73 (68)	103 (70)
Current Smoker						
YES	118 (68)	55 (50)	74 (50)	119 (67)	51 (47)	69 (47)
NO	56 (32)	54 (50)	73 (50)	59 (33)	57 (53)	78 (53)

MO Comment: I want to point out again that although the Anthonisen criteria was used for Type I patients inclusion into 065 protocol and Type I or II patients for inclusion into 064 protocol, the patients did not have pulmonary function tests done to document that in fact, there was a baseline chronic pulmonary obstructive disease (as was done in the original trial by Anthonisen where these criteria are derived from). The numbers for presenting symptoms and the duration of treatment are similar between the 5-day gatifloxacin arm and the comparator arm. It was very interesting to see who were the 37% of the patients that were excluded in the second analysis. The table above shows that for the two baseline prognostic factors, the percentages change when the patients from sites 23/24 are excluded. In fact, the 064 analysis without sites 23/24 resembles the results of 065 analysis much more closely than the original 064 analysis which included sites 23/24. Therefore together with the age disparity discussed above, the patients who were removed from the second analysis were young patients who smoked and were not as sick at baseline (just the population we should not be studying for this indication).

Table 7: Bacterial Isolates

	5-Day Gatifloxacin			Comparator		
	064 N=109	065 N=147	Total N=256	064 N=108	065 N=147	Total N=255
No. of patients with Pathogen	66 (61)	104 (71)	170 (66)	61 (56)	102 (69)	163 (64)
<i>S. pneumoniae</i> :	14	16	30	8	11	19
Pen Sensitive	12	8	20	7	10	17
Pen Intermediate	2	6	8	1	1	2
Pen Resistant	—	2	2	—	—	—
<i>S. aureus</i> :	16	32	48	17	27	44
MSSA	15	30	45	17	24	41
MRSA	1	2	3	—	3	3
<i>H. influenzae</i> :	13	16	29	8	21	29
BLA+	5	6	11	2	7	9
BLA-	8	10	18	6	14	20
<i>M. catarrhalis</i> :	12	28	40	12	19	31

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BLA+	12	27	39	12	18	30
BLA-	--	1	1	--	1	1
<i>H. parainfluenzae</i> :	8	23	31	7	23	30
BLA+	1	2	3	1	1	2
BLA-	7	21	28	6	22	28

Patients may have more than one pathogen

MO COMMENT: Microbiology reviewer (Peter Dionne) felt that the number of isolates for each of these organisms (these five were granted approval under the original AECB 7-10 days indication) were adequate for this review (as presented in the above table) even without the isolates from the excluded sites 23/24. I concur with his analysis.

Table 8: Patient Disposition

	No. (%) of Patients					
	5-Day Gatifloxacin			Comparator		
	064 N=109	065 N=147	Total N=256	064 N=108	065 N=147	Total N=255
Total Treated	105 (96)	142 (97)	247 (96)	104 (96)	138 (94)	242 (95)
Eligible	105 (96)	142 (97)	247 (96)	104 (96)	138 (94)	242 (95)
Reasons Ineligible						
No Purulent Sputum	3 (3)	3 (2)	6 (2)	2 (2)	1 (<1)	3 (1)
Less than Req. S/S	--	--	--	--	5 (3)	5 (2)
Other	--	1 (<1)	1 (<1)	2 (2)	1 (<1)	3 (1)
Positive X-ray	--	1 (<1)	1 (<1)	--	2 (1)	2 (<1)
No Bronchitis	1 (<1)	--	1 (<1)	--	--	--
Clinically Evaluable	97 (89)	127 (86)	224 (88)	101 (94)	125 (85)	226 (89)
Reasons Unevaluable						
No TOC	5 (5)	2 (1)	7 (3)	1 (1)	2 (1)	3 (1)
Ineligible	4 (4)	5 (2)	9 (4)	4 (4)	9 (6)	13 (5)
Other	--	10 (7)	10 (4)	--	6 (4)	6 (2)
Insufficient Dosage	2 (2)	2 (1)	4 (2)	2 (2)	5 (3)	7 (3)
Other Antibiotics	1 (<1)	1 (<1)	2 (<1)	--	--	--
Treated Patients with Pathogens	66 (61)	104 (71)	170 (66)	61 (56)	102 (69)	163 (64)
Eligible Patients with Pathogens	65 (60)	101 (69)	166 (65)	61 (56)	95 (65)	156 (61)
Clinically Evaluable Patients w/ Pathogens	62 (57)	91 (62)	153 (60)	59 (55)	87 (59)	146 (57)
Microbiologically Evaluable Patients	43 (39)	73 (50)	116 (45)	41 (38)	74 (50)	115 (45)

MO COMMENT: As the dataset population definitions become more stringent, the number of evaluable patients in each dataset decrease significantly so that only 40-50% of the original number of enrolled patients remain for microbiological evaluability. The efficacy analysis of these dataset populations by the applicant and by the FDA is shown in the table below.

Table 9: Clinical Efficacy (Applicant's Analysis)

	Number Cured/No. of Patients (%)					
	5-Day Gatifloxacin			Comparator		
	064 N=109	065 N=147	Total N=256	064 N=108	065 N=147	Total N=255
All Treated Patients: 95% CI	94/109 (86) (-7.8%, 10.5%)	112/147 (76) (-5.9%, 14.2%)	206/256 (80)	91/108 (84)	104/147 (71)	195/255 (76)
Eligible Patients 95% CI	92/105 (88) (-6.3%, 11.6%)	110/142 (77) (-5.2%, 15.2%)	202/247 (82)	88/104 (85)	98/138 (71)	186/242 (77)
Clinically Evaluable Patients 95% CI	86/97 (89) (-5.3%, 12.3%)	104/127 (82) (-3.4%, 17.0%)	190/224 (85)	86/101 (85)	92/125 (74)	178/226 (79)
Microbiologically Evaluable Patients 95% CI	39/43 (91) (-18.1%, 6.0%)	63/73 (86) (-3.2%, 22.2%)	102/116 (88)	38/41 (93%)	55/74 (74)	93/115 (81)

Table 10: Primary Efficacy Results (FDA analysis)

	Number Cured/No. of Patients (%)					
	5-Day Gatifloxacin			Comparator		
	064 N=107	065 N=147	Total N=256	064 N=108	065 N=147	Total N=255
Clinically Evaluable Patients 95% CI	86/97 (89) (-3.7%, 13.9%)	104/127 (82) (-1.8%, 18.6%)	190/224 (85)	86/102 (85)	92/125 (74)	178/227 (79)
Eligible Patients 95% CI	92/105 (88) (-4.8%, 13.1%)	110/142 (77) (-3.8%, 16.7%)	202/247 (82)	88/104 (85)	98/138 (71)	186/242 (77)

95% Confidence Interval for Difference in Cure Rates (Fleiss method)

Taken from Dr. Silliman's Review Tables 2.2.a.2, 2.2.b, 2.3.a.2, and 2.3.b

MO COMMENT: Cure rates were considered similar between the 5-day gatifloxacin and the comparator arms. Using the acceptable difference limit of 15%, results were fairly robust. Clinical responses were higher across both arms in study 064 than in study 065. The reason for the lower response in the latter study is not entirely clear. Study 064 allowed enrollment of less severe exacerbations (i.e., Anthonisen classification Type II and III), yet over 80% of patients (both overall and within the 5-day gatifloxacin arm) did have Type I exacerbations. The use of inhaled steroid preparations was more frequent in study 065, perhaps suggesting the presence of more severe underlying COPD among the patients in this study.

Another explanation could be the following. For both studies, BMS Medical Reviewer did use a strict algorithm for the assessment of clinical outcomes in this study-for a patient to be called a cure, improvement or resolution of all cardinal signs and symptoms was required; if a patient had only one sign or symptom that was unchanged from the pre-treatment visit they were deemed a failure, even if they did not receive additional antibiotic therapy. However, for study 065, it was noted while examining failures that gatifloxacin patients who fail might be performing more poorly than azithromycin patients who fail. Twenty-two (13 gatifloxacin, 9 azithromycin) of the 56 patients who were considered treatment failures were given additional systemic antibiotics, while the other 34 (10 gatifloxacin, 24 azithromycin) patients did not receive additional antibiotics. In other words, 13/23 (56%) patients in the gatifloxacin arm were

treated with additional antibiotics while only 9/33 (27%) patients in the azithromycin arm were treated with additional antibiotics.

To assure that the patients who were deemed failures were comparable in the severity of signs and symptoms between the two groups at the time of failing therapy, a separate analysis was done where clinically evaluable patients who had at least 2/4 signs and symptoms be improved or resolved and no sign or symptom being worse were included. This analysis in fact added more patients to azithromycin CURE group (3 additional patients for CURE in gatifloxacin group and 17 additional patients for CURE in azithromycin group (see Table 12 below).

Table 11: Study 065 Clinical Response, Clinically Evaluable Patients (Applicant's analysis)

Clinical Response	Gatifloxacin (N=127)	Number of Patients (%)	
		Azithromycin (N=125)	Total (N=252)
Cure	104 (82)	92 (74)	196 (78)
Failure	23 (18)	33 (26)	56 (22)

[gatifloxacin = 82%; azithromycin = 74%; 95% CI (-3.4%, 17.0%)]

Table 12: Study 065 Clinical Response, CE Patients (FDA's adjusted analysis)

Clinical Response	Gatifloxacin (N=127)	Number of Patients (%)	
		Azithromycin (N=125)	Total (N=252)
Cure	107 (84)	107 (87)	219 (87)
Failure	20 (16)	18 (13)	33 (13)

gatifloxacin = 84%; azithromycin = 87%;
Fleiss 95% CI (-11.5%, 5.7%)

MO continued COMMENT: In this "worst case scenerio" analysis, the adjustment resulted in the observed cure rates being much closer together than in the original analysis with the cure rates more similar to the rates seen in the 064 study. The lower bounds of the CI's even with the sensitivity adjustments are well within the pre-specified 15% limit so the overall conclusions remain the same.

The clinical response rates were also similar in the supporting trial submitted by the applicant. Briefly, the supporting trial was as follows:

[The German Company with development and marketing rights for gatifloxacin in Europe, did a single blinded study (KF5501/03) in patients with AECB. This was a three arm study comparing two 5-day regimen of gatifloxacin (200 mg or 400 mg once daily) to a 10 day course of amoxicillin/clavulanate. In general, the inclusion/exclusion criteria and definition of clinical and bacteriologic response were similar to those used in BMS Studies AI420-064 and 065. The primary efficacy endpoint, however, was the clinical response at the end of treatment, one to three days after completing study therapy; BMS assessed clinical response at the TOC visit. In the German study, the clinical response rates at the end of treatment for the "Efficacy Analyzable Population" were 87%, 83%, 81% for the 200 mg gatifloxacin, 400 mg gatifloxacin, and amoxicillin/clavulanate arms, respectively.]

Table 13: Secondary Efficacy Results

	Number Cured or Eradicated/No. of Patients (%)					
	5-Day Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
Bacteriologic Eradication Rates Microbiologically Evaluable Patients**						
<i>S. pneumoniae</i>	12/13 (92)	6/7 (86)	18/20 (90)	6/6 (100)	8/9 (89)	14/15 (93)
<i>M. catarrhalis</i>	11/11 (100)	24/26 (92)	35/37 (95)	11/11 (100)	14/16 (88)	25/27 (93)
<i>H. influenzae</i>	12/12 (100)	11/12 (92)	23/24 (96)	8/8 (100)	15/18 (83)	23/26 (88)
<i>H. parainfluenzae</i>	5/5 (100)	18/22 (82)	23/27 (85)	2/4 (50)	13/18 (72)	15/22 (68)
<i>S. aureus</i>	9/10 (90)	16/19 (84)	25/29 (86)	13/13 (100)	18/21 (86)	31/34 (91)
Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients**			% shown only			% shown only
<u>Exacerbation type</u>						
Type I	74/83 (89)	104/127(82)	(85)	73/88 (83)	92/125(74)	(77)
Type II	11/13 (85)	—	(85)	13/13 (100)	—	(100)
<u>Duration of episode</u>						
0-7 Days	41/51 (80)	57/66 (86)	(84)	50/54 (93)	39/56 (70)	(68)
>7 days	44/45 (98)	46/57 (81)	(88)	36/47 (77)	49/63 (78)	(80)
<u>Systemic Steroid Use</u>						
Yes	9/14 (64)	9/12 (75)	(69)	11/14 (79)	6/11 (55)	(72)
No	77/83 (93)	95/115 (83)	(87)	75/87 (86)	86/114 (75)	(82)
<u>Inhaled/Systemic SU</u>						
Yes	15/21 (71)	30/38 (79)	(76)	24/33 (73)	25/35 (71)	(78)
No	71/76 (93)	74/89 (83)	(88)	62/68 (91)	67/90 (74)	(80)
<u>Smoking History</u>						
Yes	72/81 (89)	81/98 (83)	(85)	72/83 (87)	69/97 (71)	(85)
No	14/16 (88)	23/29 (79)	(82)	14/18 (78)	23/28 (82)	(74)
<u>Current Smoker</u>						
Yes	46/49 (94)	51/62 (82)	(87)	40/47 (85)	48/57 (84)	(81)
No	40/48 (83)	53/65 (82)	(82)	46/54 (85)	44/68 (65)	(77)

*All patients from 064 study

** Patients excluding sites 23/24 from 064 study

MO COMMENT: In the applicant's analysis plan, the end of study cure rates are calculated by carrying forward TOC values for those patients with no data at the extended follow-up visit (i.e., cures are carried forward from the TOC visit to the end of study evaluation). If one instead assumes that patients who were lost to follow-up by the end of study are failures, the ends of study cure rates are shown as above. Results are similar between treatment groups. Bacteriologic cure rates were comparable between the 5-day gatifloxacin treated and the comparator arms. The number of organisms for each of the 5 respiratory pathogens and the eradication rates of those 5 pathogens were acceptable. For the comparator arm, Type II patients do better than Type I patients as would be expected. However, for the gatifloxacin-treated arm, the underlying symptomatology by the Anthonisen Criteria does not seem to make a difference in the outcome. Likewise, it is unclear what conclusions can be drawn from the results of "duration of episode" prognostic factor. As expected, patients who take concomitant inhaled or systemic steroids do worse than those without these concomitant medications. However, it is hard to reconcile how

current smokers would have a better outcome over non-smokers as was especially highlighted in the 064 study.

Table 14: Secondary Efficacy 064 Study -All Patients

	Number Cured or Eradicated/No. of Patients (%)					
	5-Day Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients**			% shown only			% shown only
<u>Systemic Steroid Use</u>						
Yes	9/14 (64)	9/12 (75)	(69)	11/14 (79)	6/11 (55)	(68)
No	126/137(92)	95/115 (83)	(88)	134/149 (90)	86/114 (75)	(84)
<u>Inhaled/Systemic SU</u>						
Yes	15/21 (71)	30/38 (79)	(76)	25/34 (71)	25/35 (71)	(72)
No	120/130 (92)	74/89 (83)	(89)	120/129 (93)	67/90 (74)	(85)
<u>Smoking History</u>						
Yes	120/134 (90)	81/98 (83)	(87)	130/144 (90)	69/97 (71)	(83)
No	15/17 (88)	23/29 (79)	(83)	15/19 (79)	23/28 (82)	(81)
<u>Current Smoker</u>						
Yes	94/101 (93)	51/62 (82)	(89)	97/107 (91)	48/57 (84)	(88)
No	41/50 (82)	53/65 (82)	(82)	46/54 (86)	44/68 (65)	(74)

MO COMMENT: The Applicant was asked to supply us with a closer look at the distribution of smokers and non-smokers with respect to age, race, gender, history of asthma, use of other drugs concomitantly, i.e. Beta adrenergic, anticholinergics, corticosteroids, and the presence of one of the 5 major pathogens isolated. The results provided in late June submission are summarized and shown next in Table 15.

**APPEARS THIS WAY
ON ORIGINAL**

Table15: Study 064 (+23/24)- Demography by Current Smoking Status, All Treated Patients

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

* The rest were mainly white

**Isolated at Pre-treatment

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

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

Table 16: Integrated Clinical Response (FDA analysis)

	Number Cured/No. of Patients (%)					
	5-Day Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
MITT 064: N=89 065: N=98	31/34 (91%)	41/51 (80%)	72/85 (85%)	25/26 (96%)	30/47 (64%)	55/73 (75%)
MCE 064: N=88 065: N=98	29/33 (88%)	41/51 (80%)	70/84 (83%)	25/26 (96%)	30/47 (64%)	55/73 (75%)

***MO COMMENT:** Finally, the above efficacy analysis was performed to see if the available population could be enriched for the most conservative comparison. This was an analysis performed to confirm the overall results. These MITT and MCE populations were not pre-specified. Only the patients who fulfilled the bacterial criteria of having purulent sputum and the presence of one of the three KEY respiratory pathogens (i.e. *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) were included in this analysis (see section B3 for dataset definitions). Point estimates of clinical responses are similar to the other dataset evaluations.*

D. Efficacy Conclusions

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

Integrated efficacy analysis was performed excluding the patients from sites 23 and 24 of the 064 study. Among Clinically Evaluable Patients in the two studies, the point estimate of pooled cure response was 85% for 5-day gatifloxacin treated patients and 79% for the comparator agents. The point estimate of pooled cure response for Modified Clinically Evaluable (FDA confirmatory analysis) Patients was 83% for the 5-day gatifloxacin treated patients and 75% for the comparator agents. In eligible patients in study 064, the 95% confidence intervals for the difference in clinical cure rates, 5-day gatifloxacin minus clarithromycin, were (-6.3%, 11.6%). In study 065, the 95% confidence interval for the difference in cure rates, gatifloxacin minus azithromycin, was (-5.2%, 15.2%) in eligible patients. Gatifloxacin eradicated 18/20 (90%) evaluable *S. pneumoniae* isolates; the comparator agents eradicated 14/15 (93%) *S. pneumoniae*. Gatifloxacin and the comparators demonstrated activity against the other two key respiratory pathogens, *H. influenzae* (23/24, 96% vs 23/26, 88%) and *M. catarrhalis* (35/37, 95% vs 25/27, 93%).

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Gatifloxacin was well-tolerated in these two studies, with an overall incidence of drug-related adverse events of 25% (compared to 22% for the pooled comparators); the most frequently occurring were diarrhea, nausea, and dry mouth. The majority of adverse events were mild to moderate in severity. Laboratory abnormalities were uncommon, as were abnormalities that reached a level of clinical significance.

B. Description of Patient Exposure

Sixty-eight investigator throughout the United States enrolled a total of 828 patients (this includes patients from sites 23/24), 821 of whom were treated. Four hundred and ninety-six patients received gatifloxacin; three hundred and twenty-one received a 5-day course and 175 received a 7-day course. Three hundred and twenty-five patients received a comparator agent (178 clarithromycin, 147 azithromycin). Just over half of the patients in each arm were male; the median age was 48 for gatifloxacin-treated patients with a range of 18-85 years and 50 for comparator-treated patients, with a range of 18-86 years. Approximately 20% of patients in each arm were elderly (age > 65 years) and between 5-8% were 75 years or older. The majority of patients were White; roughly one quarter were Black.

Study design contributed to differences in mean treatment duration. Study 064, with its clarithromycin comparator arm and double dummy design, had a mean treatment duration of 10 days; seventeen patients (i.e. 8 on 5-day gatifloxacin and 9 on clarithromycin) of this study took fewer than the prescribed 10 doses of medication. The mean duration of treatment in study 065 was 5 days; a total of 15 patients (5 gatifloxacin, 9 azithromycin) took fewer than 5 doses. Early treatment discontinuations were seen in 2% of the gatifloxacin patients and 4% of those treated with one of the two comparator agents (table below).

Table 17: Treatment Discontinuations

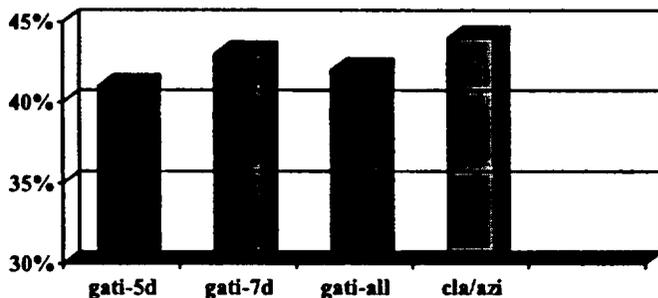
	No. (%) of Patients					
	5-Day Gatifloxacin			Comparator		
	064 N=174	065 N=147	Total N=321	064 N=178	065 N=108	Total N=147
Reasons for Early Discontinuations						
Adverse Event	2 (1)	2 (1)	4 (1)	4 (2)	4 (3)	8 (2)
Non-Qualifying Gram Stain	1 (<1)	--	1 (<1)	2 (1)	--	2 (<1)
Patient Request	1 (<1)	--	1 (<1)	--	--	--
Subject Noncompliant	--	1 (<1)	1 (<1)	--	--	--
Evidence of Pneumonia	--	--	--	--	1 (<1)	1 (<1)
Other Antibiotic	--	--	--	--	1 (<1)	1 (<1)
Protocol Violation	--	--	--	--	1 (<1)	1 (<1)
Total Early Discontinuations	4 (2)	3 (2)	7 (2)	6 (3)	7 (5)	13 (4)

C. Methods and Specific Findings of Safety Review

All adverse clinical events, drug related adverse events, death and serious adverse events, adverse events leading to discontinuation of study therapy, and laboratory study results were reviewed via applicant's tables, narratives, electronic datasets, and randomly selected 10% of the case report forms. For death and

serious adverse event, and adverse events leading to discontinuation of study therapy, approximately 1/3 of the case report forms were randomly selected and reviewed in detail for concurrence with applicant's narratives and tables.

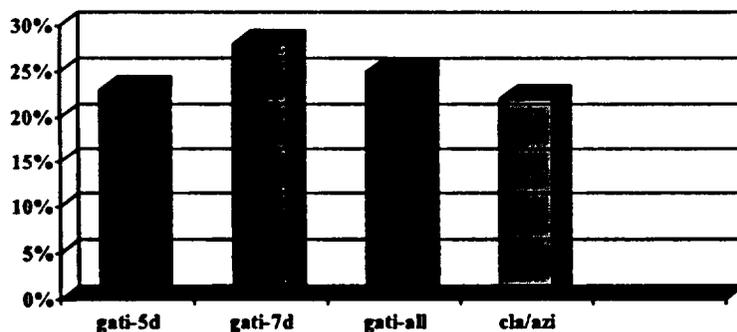
C.1s Adverse Clinical Events of All Causes



AE/exposed 132/321 75/175 208/496 143/325

The incidence of adverse events of all causes in the gatifloxacin arms was comparable to that seen in the pooled comparator arm (clarithromycin/azithromycin). The most frequent events among gatifloxacin treated patients were coughing, diarrhea, and nausea (6% each), while diarrhea (9%) and headache (6%) were most frequent in the pooled comparator arm. [See Table 26 of Appendix 1 and Table 20 of Appendix 2 for listing of most frequent adverse events of all causes]

C.2s Drug-related Adverse Clinical Events



DAE/exposed 75/321 49/175 124/496 70/325

Diarrhea (5%), nausea (5%) and dry mouth (4%) were the most frequently noted study-drug related adverse events for patients in the pooled gatifloxacin arm. Diarrhea (6%), taste perversion (5%) and nausea (4%) were the most frequently reported drug-related adverse events in the comparator arm. In most cases, the incidence of events was comparable in the 5 and 7 day gatifloxacin arms. Vaginitis was reported by 2% of the women in both comparator and gatifloxacin patient populations. [see Tables 27A and 27B of Appendix 1 and Table 21 of Appendix 2 for listing of most frequent drug-related adverse events]

Majority (94%, 117/124) of gatifloxacin-treated patients had drug-related adverse events judged to be mild or moderate in severity. There were six events judged to be severe; two cases each of diarrhea and vaginitis, and one case each of nausea and dry mouth. One patient 004-077 in the 065 protocol treated with gatifloxacin had an adverse event judged to be very severe. He developed right buttock spasms two days after finishing his 5 day course of therapy. The symptom was reported as very severe 3 weeks later, but did not require treatment as per the applicant.

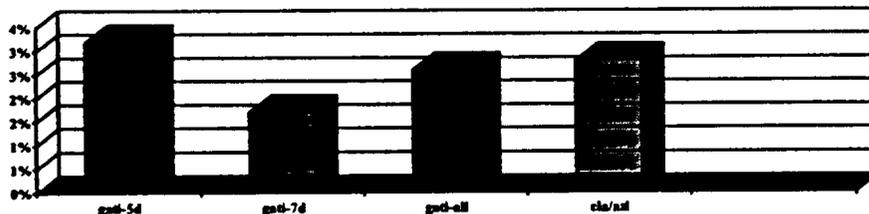
C.3s Laboratory Abnormalities in Patients with Normal Baseline Values

The development of Grade 3 or above laboratory abnormalities in patients with normal baseline values was uncommon in these studies. The most frequently observed abnormalities were: hyponatremia (15% gatifloxacin, 13% comparator), and increased bicarbonate (11%, gatifloxacin, 12% comparators). The two abnormalities seen only in gatifloxacin-treated patients were hypoglycemia (1 patient) and hyperglycemia (4 patients); all received five days of gatifloxacin. The majority of laboratory abnormalities were Grade 1 in severity. Grade 3 abnormalities occurred in 5 patients. These abnormalities included a female with an elevated AST (064-037-257, 5-day gatifloxacin arm). This patient had AST levels elevated to 228 U/L from baseline normal values. She had no physical history that would explain the elevated AST levels and no follow-up values were obtained), two males with neutropenia (064-024-875, 7-day gatifloxacin; 065-034-221, azithromycin), and a male (064-024-756) and female (064-050-583) with hypochloremia. There were no Grade 4 laboratory abnormalities.

C.4s Laboratory Abnormalities in Patients with Abnormal Baseline Values

Among those patients who were enrolled in these studies with abnormal laboratory values, worsening results were uncommon. In the pooled gatifloxacin arm, the most frequent laboratory abnormalities were increasing AST (7/65 tested patients), worsening hypochloremia (6/15), and worsening hyponatremia (5/77). For the comparator arm, the most frequent worsening laboratory values were increasing AST (8/37 tested), and neutropenia (3/8). Grade 3 or 4 abnormal values were uncommon, developing in six gatifloxacin-treated patients and four comparator-treated patients. One patient in each group (065-012-343, 5-day gatifloxacin; 065-031-295, azithromycin) developed Grade 4 elevation in serum glucose. Both patients were diabetic and both elevations to Grade 4 (310 to 524 mg/dL – gatifloxacin patient and 154 to 516 mg/dL – azithromycin patient) did not have a follow-up level recorded.

C.5s Serious Adverse Events



SAE/exposed 10/321 3/175 13/496 9/325

Three percent of the 821 patients treated in these two studies experienced serious adverse events. The incidence was identical in the pooled comparator and gatifloxacin treatment arms. Problems of a respiratory nature-such as hospitalizations for the presenting infection, or the development of pneumonia-accounted for the majority of these events.

There was one death that occurred within 30 days of the last dose of study therapy.

"Patient 051-420 was a seventy-five year-old male with a past medical history of BPH and 'stable leukemia', for which he was not receiving treatment. At the time of his randomization to gatifloxacin on 14 April 2000, his white blood cell count was 52,000, with 15% neutrophils and 82% lymphocytes. His pre-treatment sputum culture was positive for *S. marcescens*. He completed therapy on 18 April and reported improvement in all four cardinal signs and symptoms during the telephone contact on 21 April. When he missed his next scheduled appointment on 27 April, several unsuccessful attempts were made to reach him. On 4 May, the patient's wife phoned the site to inform study staff that the patient had been admitted to the hospital on 27 April with pneumonia, and had died that same day of respiratory failure and cardiac arrest. An autopsy was not performed" (taken from page 123, volume 5 of the Supplemental NDA).

C.6s Discontinuations Due to Adverse Events and Laboratory Abnormalities

A total of sixteen patients (eight treated with gatifloxacin, eight with comparators) discontinued study therapy because of adverse events (see Table 17). Among gatifloxacin-treated patients who stopped treatment because of adverse events, respiratory tract symptoms, such as cough and dyspnea were more common in the 5-day treatment arm. Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, were more frequently cited as a reason for discontinuation in the 7-day arm, and were the most frequent cause of discontinuation in the pooled comparator arm. There were no discontinuations of therapy due to laboratory abnormalities.

MO COMMENT: Most adverse events in these studies were non-serious in nature. Quinolone-class related events, namely phototoxicity, tendinitis, seizures, and cardiac symptoms, were not encountered. Upon review of the narrative summaries and the case report forms, I agree with the applicant's assessments that these serious adverse events including the one death case above (limited information provided however) are most likely unrelated to the drug trial at hand. Also, this was a low incidence of serious adverse events and the numbers similar in the comparator arm.

Overall, gatifloxacin appears to have a favorable adverse event profile in terms of laboratory parameters. Comparable and low numbers of abnormalities were seen in all arms. The one laboratory abnormality where unequal numbers resulted was in glucose abnormalities. Five patients without baseline abnormal laboratory values developed mild glucose abnormalities in the gatifloxacin-treated arm versus none in the comparator-treated arm. Thus, the one adverse event which may need to be better monitored in future trials is blood sugar levels, especially in light of post-marketing adverse event reports of significant hyperglycemic and hypoglycemic events (see Appendix 3). Abnormalities in liver function tests were not severe.

VIII. Dosing, Regimen, and Administration Issues

The drug dosing regimen is changed from 7-10 days down to 5-day duration. Otherwise, there are no changes from the original NDA for this indication.

XI. Use in Special Populations

A. Evaluation of Applicant's Gender Effects Analyses and Adequacy of Investigation

There was no gender distinction in enrollment with the exception of excluding females who were pregnant or lactating. As a result, just over half of the all patients randomized and assessed were male. In the efficacy analysis, separate results were not presented by gender. However, in the safety analysis, the applicant presented all analysis with a separate analysis for gender. Thus, for adverse events of all causes, 46% of females and 38% of males experienced adverse clinical events. In addition to occurrence of vaginitis, this difference was accounted for by a higher incidence of coughing, chest pain, and nausea