

The medical officer reviewed and agreed with the sponsor's designation of all patients designated as ineligible or unevaluable for the reasons outlined above. The 7 patients listed as ineligible under the "Other" category included six patients with a history of chronic sinusitis (an exclusion criterion) and one patient who had radiological documentation of sinusitis only after 13 days in the study.

### 8.3.2.9.6 Efficacy

#### *Clinical Efficacy*

The following table was obtained from the NDA (Amendment 20, Volume 1, pg. 93):

#### Clinical Response, Clinically Evaluable Patients Protocol AI420-007

	Number (%) of Patients			95% C.I.
	U.S. Sites N = 252	Non-U.S. Sites N = 87	Total N = 339	
Clinical Response				
Cured	200 (79)	76 (87)	276 (81)	(76.9%, 85.4%)
Failure	52 (21)	11 (13)	63 (19)	

NOTE: C.I. = Confidence Interval on overall cure rate.

**MO Comment:** The clinical response rate was notably higher in this study compared to the AI420-008 study (72% by sponsor's analysis). This may be attributed, in part, to: 1) enrollment in ex-USA study sites, which demonstrated higher response rates in this study compared to US sites, and 2) the open-label non-comparative design.

The medical officer reviewed the clinical efficacy and signs/symptoms datasets. The medical officer agreed with the sponsor's designation of "failure" in all cases. All but one of the patients designated by the sponsor as a clinical cure had complete resolution or improvement in the cardinal signs/symptoms of their infection (i.e., purulent nasal discharge and sinus pain or tenderness). The remaining patient (00004 00012) had nasal purulent discharge, nasal congestion, and facial pressure rated as "same" and headache rated as "worse" at the test of cure visit. This patient was labeled as early relapse by the investigator, but was listed as "cured" in the efficacy data set. Reassignment of this patient as a treatment failure did not alter the overall response rate of 81%.

*Bacteriological Efficacy*

The overall bacteriological eradication rate for the microbiologically evaluable patients was 82%. Clinical cure responses matched microbiological eradication in all infections caused by the three major sinusitis pathogens with only one exception. Patient 007-002 with a documented had resolution of all signs and symptoms of the acute infection but was given antibiotic due to residual abnormalities on followup sinus x-rays. This patient was designated as a clinical failure, but a bacteriologic success. The following table was obtained from the NDA (Amendment 20, Volume 1, pg. 102):

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**Bacteriologic Eradication Rate by Pathogen, Non-Resistant Pathogens from  
Microbiologically Evaluable Patients  
Protocol AI420-007**

Pathogen <sup>a</sup> /Subtype	Number Eradicated/Number Isolated (%)		
	U.S. Sites	Non-U.S. Sites	Total
<i>S. pneumoniae</i>	19/22 (86)	20/22 (91)	39/44 (89)
Penicillin Susceptible	10/10 (100)	13/14 (93)	23/24 (96)
Penicillin Intermediate	6/7 (86)	1/2 (50)	7/9 (78)
Penicillin Resistant	2/3 (67)	4/4 (100)	6/7 (86)
Penicillin Susceptibility Unknown	½ (50)	2/2 (100)	¾ (75)
<i>H. influenzae</i>	11/15 (73)	6/7 (86)	17/22 (77)
β-Lactamase -	6/8 (75)	2/3 (67)	8/11 (73)
β-Lactamase +	5/7 (71)	4/4 (100)	9/11 (82)
<i>M. catarrhalis</i>	1/3 (33)	3/3 (100)	4/6 (67)
β-Lactamase -	-	1/1 (100)	1/1 (100)
β-Lactamase +	1/3 (33)	2/2 (100)	3/5 (60)
<i>S. aureus</i>	13/15 (87)	8/10 (80)	21/25 (84)
Methicillin Susceptible	11/13 (85)	5/7 (71)	16/20 (80)
Methicillin Resistant	-	3/3 (100)	3/3 (100)
Methicillin Susceptibility Unknown	2/2 (100)	-	2/2 (100)
Other Gram-positive <sup>b</sup>	7/8 (88)	0/1	7/9 (88)
Other Gram-negative <sup>c</sup>	25/29 (86)	8/8 (100)	33/37 (89)
<b>TOTAL</b>	<b>76/92 (83)</b>	<b>45/51 (88)</b>	<b>121/143 (85)</b>

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

<sup>b</sup> Consisted of four different organisms at U.S. sites and one organism at a non-U.S. site.

<sup>c</sup> Consisted of 11 different organisms at U.S. sites and six different organism at a non-U.S. sites.

Indication: Acute Sinusitis

Revision Date: 21-Oct-99

MO Comment: The bacteriological eradication rates for *Streptococcus pneumoniae* and *Haemophilus influenzae* ( $\beta$ -lactamase + and -) are acceptable. While gatifloxacin appeared to demonstrate activity against six of seven penicillin resistant *S. pneumoniae* infections, the small number of isolates in this study would be insufficient to support labeling for resistant organisms. Similarly, only six microbiologically evaluable patients with *Moraxella catarrhalis* isolates were enrolled in the study with an overall eradication rate of 67%. Only one of three *M. catarrhalis* infections from U.S. study sites was microbiologically eradicated. Unfortunately, no other microbiological data from a similar closed space site of infection (e.g., acute otitis media) was submitted with the NDA. The sponsor presents an eradication rate of 84% (21/25) for *Staphylococcus aureus* in the table above, although they have not requested this organism in the proposed labeling for the acute sinusitis indication. The FDA has not yet granted an indication for this organism in acute bacterial sinusitis due to the difficulty in establishing its role as a pathogen (rather than a specimen contaminant) since *S. aureus* can be part of the resident nasal flora. The draft DAIDP evaluability criteria guidance document for acute sinusitis specifies that *S. aureus* isolates will be considered pathogenic only if isolated in pure culture with colony counts  $\geq 10^3$  CFU/mL. In summary, the microbiological efficacy data from this study would support labeling for acute sinusitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, but not *Moraxella catarrhalis*.

(Note: FDA has previously approved CEFTIN® for acute maxillary sinusitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (non-beta-producing lactamase producing strain only).

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## 8.3.2.9.7 Safety

*Deaths*

There were no deaths during the study.

*Serious Adverse Events*

Four serious adverse events were recorded during the study. Only the last one listed below was felt by the investigator to have possible relationship to the study drug.

Study Drug	Patient No.	Study Day	Serious Adverse Event
Gatifloxacin	008-005	4	Admission for alcohol detoxification
Gatifloxacin	014-004	+19	Hospitalization for aspiration following drug overdose
Gatifloxacin	040-015	+4	Hospitalization for flare of pre-existing bronchiectasis
Gatifloxacin	040-002	2	Unintentional gatifloxacin overdosage; elevated-serum glucose requiring hospitalization (h/o diabetes mellitus)

MO Comment: The association of gatifloxacin overdosage with hyperglycemia in patient 040-002 highlights the importance of systematically evaluating the drug's effects on serum glucose levels across all studies in the NDA. As stated earlier, these data will be presented in the Integrated Safety Summary (Dr. Korvick).

*Adverse Events*

Overall, 254 of treated patients (57%) experienced at least one adverse clinical event, and in 135 of these patients the event was considered to be related to study drug therapy. Please refer to the NDA (Amendment 20, Volume 1, page 110) for a complete listing of all adverse clinical events.

The following table from the NDA (Amendment 20, Volume 1, page 112) shows drug-related adverse clinical events occurring in  $\geq 1\%$  of treated patients:

**Drug-Related Adverse Clinical Events by Severity,  
All Treated Patients  
Protocol AI420-007**

Adverse Clinical Event <sup>a</sup>	Number (%) of Patients (N = 443)				
	Mild	Moderate	Severe	Very Severe	Total
<u>Any Drug-Related Adverse Clinical Event</u>	69 (16)	60 (14)	6 (1)	0	135 (30)
Nausea	22 (5)	12 (3)	0	0	34 (8)
Vaginitis <sup>b</sup>	12 (3)	10 (2)	0	0	22 (8)
Diarrhea	12 (3)	4 (< 1)	0	0	16 (4)
Dizziness	8 (2)	6 (1)	1 (< 1)	0	15 (3)
Dyspepsia	6 (1)	6 (1)	1 (< 1)	0	13 (3)
Flatulence	6 (1)	7 (2)	0	0	13 (3)
Headache	5 (1)	3 (< 1)	2 (< 1)	0	10 (2)
Rhinitis	6 (1)	3 (< 1)	1 (< 1)	0	10 (2)
Pain Abdomen	4 (< 1)	2 (< 1)	1 (< 1)	0	7 (2)
Taste Perversion	4 (< 1)	2 (< 1)	0	0	6 (1)
Dry Mouth	4 (< 1)	1 (< 1)	0	0	5 (1)
Somnolence	4 (< 1)	1 (< 1)	0	0	5 (1)

<sup>a</sup> All drug-related adverse clinical events occurring in  $\geq 1\%$  of patients.

<sup>b</sup> Percentage based on the number of females.

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Fifteen patients discontinued the study due to adverse events, most frequently due to gastrointestinal events: nausea (4), diarrhea (2), abdominal pain(2), dyspepsia (1), gastritis (1). Two patients discontinued to events likely related to an immediate hypersensitivity reaction. Patient 053-019 experienced itching and welts on his torso and extremities after a single dose of study drug. Patient 056-025 developed hives on day 1 of treatment that led to discontinuation of study drug after the third dose. Both events resolved with antihistamine therapy.

MO Comment: The medical officer's analysis of the adverse clinical events dataset yielded very similar results to the table above. As shown above, adverse events were most commonly related to the gastrointestinal tract and were mild or moderate in severity. Of note, two patients with probable Type I hypersensitivity reactions (hives) had to be discontinued from the study. As seen in the two gatifloxacin-treated patients from the A1420-008 study with possible allergic reactions, both patients in this study were treated conservatively with complete resolution of the events. Review of post-marketing adverse events for gatifloxacin should include a heightened awareness of Type I hypersensitivity reactions.

*Clinical Laboratories*

From the NDA (Amendment 20, Volume 1, page 118):

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**Abnormal Laboratory Test Values During or Post-Treatment in All Treated  
Patients with Normal Pre-treatment Values  
Protocol AI420-007**

Laboratory Test	Number (%) of Patients (N = 443)				
	Na	Grade 1	Grade 2	Grade 3	Grade 4
<u>Hematology</u>					
Hemoglobin	377	29 (8)	1 (<1)	0	0
WBC	416	11 (3)	2 (<1)	0	0
Neutrophils	412	16 (4)	3 (<1)	1 (<1)	0
Platelets	411	12 (3)	0	0	0
<u>Liver Function</u>					
AST	393	18 (5)	0	0	0
ALT	375	19 (5)	1 (<1)	0	0
Total Bilirubin	408		11 (3)	1 (<1)	0
Alkaline Phosphatase	389	9 (2)	0	0	0
<u>Renal Function</u>					
BUN	415	6 (1)	0	0	0
Creatinine	417	9 (2)	1 (<1)	1 (<1)	0
<u>Metabolic</u>					
Hypoglycemia	63	2 (3)	1 (2)	0	0
Hyperglycemia	63	3 (5)	1 (2)	0	0
<u>Pancreatic Function</u>					
Amylase	373	12 (3)	1 (<1)	0	0
<u>Electrolytes</u>					
Hyponatremia	382	37 (10)	0	0	0
Hypernatremia	382	6 (2)	3 (<1)	0	0
Hypokalemia	402	5 (1)	0	0	0
Hyperkalemia	402	3 (<1)	4 (<1)	1 (<1)	0
Hypochloremia	397	3 (<1)	2 (<1)	0	0
Hyperchloremia	397	8 (2)	2 (<1)	0	0
Bicarbonate Decrease	254	41 (16)	2 (<1)	0	0
Bicarbonate Increase	254	32 (13)	0	0	0

A For each test, number of patients with a normal pre-treatment value who had at least one during- or post-treatment value determined.

Indication: Acute Sinusitis

Revision Date: 21-Oct-99

MO Comment: As seen in Study AI420-008, the most common abnormality noted on clinical labs were hyponatremia and alteration in serum bicarbonate levels. Of the 443 patients taking gatifloxacin, only three developed Grade 3 lab abnormalities (1 hyperkalemia, 1 elevated bilirubin, 1 elevated amylase); none developed a Grade 4 abnormality during the course of the study. There were thirty-five Grade 2 abnormalities; these included eleven patients with elevated total bilirubin. For five of these patients, the values returned to normal; for the other six, no follow-up information is available.

\*Note: The Grade 3 abnormality in serum creatinine in the sponsor's table above reflects a transcription error at the study site. The patient's creatinine at the end of the study was recorded as 5.2 in the NDA database. The medical officer queried the sponsor regarding follow-up on this patient. In a faxed message to FDA dated September 10, 1999, the sponsor explained that the creatinine value was actually 1.2 but was incorrectly transcribed.

### 8.3.2.10 Medical Officer's Summary/Conclusions

This open-label, non-comparative study focused on gatifloxacin's bacteriological eradication rates for the major pathogens in acute sinusitis. A total of 445 patients were enrolled from 28 sites in the United States, Mexico, Argentina, Australia, and South Africa. All patients underwent antral puncture to document microbial etiology of infection. The sponsor considered 339 of these patients (77%) to be clinically evaluable and 119 (27%) to be microbiologically evaluable.

The sponsor's clinical response rate at the test of cure visit (day +19 to +30 post-therapy) was 81%, 95% C.I. = (76.9%, 85.4%). The clinical response rate was notably higher in this study compared to the AI420-008 study (cure rate per sponsor's analysis = 72%). This may be attributed, in part, to: 1) enrollment in ex-USA study sites, which demonstrated higher response rates in this study compared to US sites, and 2) the open-label non-comparative design. The medical officer concurred with the sponsor's assignment of clinical response in nearly all cases.

The overall bacteriological eradication rate for the microbiologically evaluable patients was 82%. Eradication rates for *Streptococcus pneumoniae* and *Haemophilus influenzae* were 89% (39/44) and 77% (17/22), respectively. Only six microbiologically evaluable patients with *Moraxella catarrhalis* isolates were enrolled in the study with an overall eradication rate of 67% (4/6). While gatifloxacin appeared to demonstrate activity against six of seven penicillin resistant *S. pneumoniae* infections, the small number of isolates in this study would be insufficient to support labeling for resistant organisms. Thus, the microbiological efficacy data from this study would support labeling for *Streptococcus pneumoniae* and *Haemophilus influenzae*, but not *Moraxella catarrhalis*.

The safety profile of gatifloxacin in this study was similar to that in Study AI420-008. The majority of drug-related adverse events were related to the gastrointestinal tract (nausea, diarrhea, dyspepsia and abdominal pain) and were mild in severity. Of note, two patients with probable Type I hypersensitivity reactions (hives) had to be discontinued from the study. Review of post-marketing adverse events for gatifloxacin should include a heightened awareness of Type I hypersensitivity reactions. Clinical laboratory abnormalities were generally uncommon and mild (Grade 1 or 2).

The medical officer concludes that this study supports approval of the acute sinusitis indication within the NDA. Specifically, the microbiological data supports labeling of gatifloxacin for the treatment of infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae*. However, insufficient isolates of *Moraxella catarrhalis* were obtained to support the proposed labeling for this organism. The safety profile for gatifloxacin from this study is acceptable.

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### 8.3.3 Study No. AI420-066: "A Randomized, Double-Blind Multi-center Comparison of Gatifloxacin to Trovafloxacin in the Treatment of Subjects with Acute Uncomplicated Maxillary Sinusitis"

#### 8.3.3.1 Objectives:

The protocol-specified objectives of this study were to:

- Compare the efficacy of gatifloxacin, 400 mg PO QD for 10 days, to a regimen of trovafloxacin, 200 mg PO QD for 10 days;
- Evaluate the safety profile of gatifloxacin relative to trovafloxacin in this patient population;
- Evaluate the impact of the treatment of sinusitis with gatifloxacin relative to trovafloxacin on medication adherence, symptoms and functional status assessment; and
- Assess the pharmaco-economic profiles of gatifloxacin relative to trovafloxacin in the treatment of acute maxillary sinusitis, including cost-effectiveness analysis and cost of an event-free cure.

MO Comment: During the design and conduct of this study, trovafloxacin had an approved indication for acute sinusitis caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* and was an appropriate choice for a comparator drug. However, post-marketing experience with trovafloxacin has recently been associated with serious liver injury in some patients leading to liver transplantation and/or death. After consultations with the FDA, the sponsor has revised the product label to include the following statements in a black box warning:

**"... TROVAN SHOULD BE RESERVED FOR USE IN PATIENTS WITH SERIOUS, LIFE- OR LIMB-THREATENING INFECTIONS WHO RECEIVE THEIR INITIAL THERAPY IN AN IN-PATIENT HEALTH CARE FACILITY (I.E., HOSPITAL OR LONG-TERM NURSING CARE FACILITY). TROVAN SHOULD NOT BE USED WHEN SAFER, ALTERNATIVE ANTIMICROBIAL THERAPY WILL BE EFFECTIVE."**

While safety concerns currently contraindicate the product's use in uncomplicated, acute sinusitis, the efficacy and safety data obtained from this comparative clinical trial is still valid in supporting the NDA. The proposed comparisons of pharmaco-economic profiles, adverse events, treatment compliance, and functional assessment for the two drugs will obviously be of limited promotional value for this indication.

#### 8.3.3.2 Protocol Overview

This was a randomized (1:1), double-blind, multicenter study designed to assess the safety and efficacy of gatifloxacin, 400 mg PO QD for 10 days, compared to trovafloxacin, 200 mg PO QD for 10 days, in the treatment of

adults with acute, uncomplicated maxillary sinusitis for whom oral, outpatient therapy was indicated.

The study was conducted at 26 study sites in the United States from October 12, 1998 through January 20, 1999. The study was conducted in conjunction with the contract research organization [REDACTED]

#### 8.3.3.3 Inclusion Criteria

See above review of Study AI420-008 – the criteria and MO Comments are identical.

#### 8.3.3.4 Exclusion Criteria

Patients were excluded if they met any of the following criteria:

- Chronic presentation of the current episode of sinusitis (duration of signs and symptoms of sinusitis longer than 28 days);
- Presence of complicated sinusitis (e.g., Pott's puffy tumor, malignancy involving the sinus, osteomyelitis, contiguous bone infection, or requiring reconstructive surgery);
- Presence of an anatomic abnormality involving the maxillary sinus ostium that would impair drainage of the sinus and that might affect the response to therapy (e.g., post-traumatic or post-surgical defect);
- Recent sinus surgery (i.e., within three months before enrollment);
- Nosocomial sinusitis secondary to head trauma or nasotracheal intubation;
- Receipt of greater than a single dose of any systemic antibiotic within the 7-day period prior to enrollment, or likelihood of receiving other systemic antibiotics during the study;
- Long-term (greater than 10 days) antibacterial therapy needed, in Investigator's opinion;
- History of cystic fibrosis;
- Previously diagnosed disease(s) of immune function (e.g., AIDS or history of clinical manifestations of HIV infection, neutrophil count  $<1000/\text{mm}^3$ );
- Current clinically significant hepatic disease (i.e., aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] and/or total bilirubin  $\geq 3$  times the upper limit of normal);

- Known renal insufficiency (e.g., creatinine clearance  $\leq$  40 mL/min or requiring renal dialysis);
- History of a serious hypersensitivity reaction to any quinolone compound;
- Malabsorption syndromes or other gastrointestinal disturbances that would affect drug absorption;
- Pregnancy and/or breast feeding; or
- Female of child bearing potential and not using an adequate birth-control method.

**MO Comment:** The inclusion/exclusion criteria are acceptable.

#### 8.3.3.5 Randomization/Blinding

This study was randomized using a permuted block design with a block size of four, unlike the dynamic randomization procedure used in Study AI420-008. Study medication was administered in a double-blind, "double-dummy" fashion. The blister cards for each treatment arm contained the appropriate combination of active drug and placebo for 10 days of QD treatment. Unblinding of all patients in the study did not occur until all data were reviewed, data entry was completed, and the database was locked. The blind was only broken in the event of a medical emergency in which the investigator felt that a patient's safety would be compromised by the blind.

**MO Comment:** The study was adequately randomized and blinded.

#### 8.3.3.6 Study Procedures/Observations

As shown in the flowchart below from the NDA submission (Amendment 15, Volume 1, page 34), the scheduled visits and procedures for this study were similar to protocol AI420-066. However, the primary clinical response determination was performed at the Post-Treatment Visit (Day +7 to Day +14) and the Extended Follow-up Visit was performed by telephone contact.

**Flow Chart: Schedule of Patient Assessments**  
**Protocol AI420-066**

Procedure	<u>Pre-Treatment</u> (within 48 hrs prior to dosing)	<u>During Treatment</u> (Days 1 through 10) <sup>i</sup>	<u>During Treatment</u> (Days 3 to 5) <sup>b</sup>	<u>End of Treatment</u> (Days +1 to +3 <sup>ab</sup> )	<u>Post-Treatment</u> (Days +7 to +14)	<u>Extended Follow-up</u> (Days +21 to +28) <sup>b</sup>
Informed Consent	X	-	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-	-
Sinus Radiograph	X	-	-	-	X <sup>e</sup>	-
Medical History <sup>c</sup>	X	-	-	-	-	-
Physical Exam	X	-	-	-	X	-
Nasal Exam	X	-	-	-	X	-
Vital Signs <sup>d</sup>	X	-	-	-	X	-
Clinical Signs and Symptoms	X	-	X <sup>b</sup>	X <sup>b</sup>	X	X <sup>b</sup>
Laboratory Tests	X	-	-	-	X <sup>e</sup>	-
Clinical Response Determination	-	-	-	-	X	-
MA/S/F <sup>g</sup> Diary Card	-	X	-	-	-	-
Adverse Event Reporting	-	-	X	X	X	X
Assess Medication Use	-	-	X	X	X	-
Pregnancy Test	X	-	-	-	X	-

a Patients discontinuing study therapy prematurely will have their post-treatment procedures done at the time of termination

b Telephone contact

c Includes assessment of sinusitis history

d Blood pressure, pulse, respiratory rate, and temperature

e If clinically indicated (i.e., all abnormal during/post-treatment laboratory test results should be repeated until they return to pre-treatment levels)

f For women of childbearing potential

g Medication adherence, symptoms and functional status assessment

h Symptoms only

i Patient diary card

**MO Comment: The study design outlined above is consistent with the current DAIDP draft guidance document regarding evaluability criteria for acute sinusitis trials (i.e., a single test of cure visit approximately 1-2 weeks following completion of therapy).**

### 8.3.3.6 Evaluability Criteria

The sponsor identified two study populations of interest using the following evaluability criteria:

All Treated Patients: All those who were randomized and who received at least one dose of study medication.

Clinically Evaluable Patients: All patients who met the following criteria:

- Met all inclusion criteria and none of the exclusion criteria;
- Received a 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.

MO Comment: The evaluability criteria are acceptable. The sponsor did not define an "Eligible Patients" population as in the A1420-008 study.

#### 8.3.3.7 Statistical Analyses

##### *Sample Size and Power*

The protocol specified that 200 evaluable patients were needed in order to have 90% power to conclude that the clinical cure rate for gatifloxacin was not inferior to trovafloxacin by more than 20%. This was based on the assumption that both treatments had equivalent cure rates of 75% and a two-sided significance level of 5%. The evaluability rate was assumed to be 85%; the total enrollment was to be 236 patients.

The sponsor's intent for the study was to show that gatifloxacin is no more than 15% inferior to trovafloxacin. Assuming 200 evaluable patients and equivalent cure rates, the power to draw this conclusion is 84% if the common cure rate is 85%, 76% if the common cure rate is 80%, and 69% if the common cure rate is 75%.

##### *Primary Efficacy Analysis*

The primary efficacy analysis was performed on the Clinically Evaluable Patients. The clinical cure rates for gatifloxacin and trovafloxacin, at both Test of Cure and End of Study, were compared. A two-sided 95% confidence interval for the difference in clinical cure rates between treatment groups was constructed using an exact method (StatXact-3<sup>®</sup>). If the two-sided 95% confidence interval for the difference in rates (gatifloxacin minus trovafloxacin) remained above a lower bound of -15%, the sponsor concluded clinical equivalence. An analysis on All Treated Patients was also performed.

### 8.3.3.8 Study Results

#### 8.3.3.8.1 Patient Population

As per the Table below (from NDA Amendment 15, Volume 1, pg. 54), two hundred fifty-five patients were randomized at 25 centers across the United States. All but one patient received at least one dose of study drug. An additional patient received one dose of study drug but was immediately discontinued from the study due to a positive serum pregnancy test. In error, the record of the single dose that this patient took was not included in the locked analysis database or in the table below.

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**Patient Disposition**  
**Protocol AI420-066**

Site Number/ Investigator	Randomized	All Treated	Clinically Evaluable
009 G. McCullouch	20 (100)	20 (100)	17 (85)
012 E. Riffer	20 (100)	20 (100)	17 (85)
008 W. Jannetti	20 (100)	19 (95)	17 (85)
002 R. Bettis	20 (100)	19 (95)	16 (80)
017 J. M. Bundy	12 (100)	12 (100)	12 (100)
016 J. Sullivan	12 (100)	12 (100)	12 (100)
011 A. Puopolo	12 (100)	12 (100)	11 (92)
015 W. Sokol	12 (100)	12 (100)	11 (92)
023 J. Rosen	12 (100)	12 (100)	11 (92)
018 S. Hausman-Cohen	11 (100)	11 (100)	10 (91)
003 E. Bolster	11 (100)	11 (100)	9 (82)
007 A. Heller	10 (100)	10 (100)	10 (100)
001 J. Adelglass	8 (100)	8 (100)	8 (100)
022 W. M. Gooch	8 (100)	8 (100)	8 (100)
006 J. B. Gregorio	8 (100)	8 (100)	8 (100)
026 J. Jacobs	8 (100)	8 (100)	8 (100)
025 M. Suchyta	8 (100)	8 (100)	7 (88)
019 S. Bowman	8 (100)	8 (100)	6 (75)
010 M. Peshiman	7 (100)	7 (100)	7 (100)
014 G. Settupane	7 (100)	7 (100)	7 (100)
013 N. Schultz	7 (100)	7 (100)	5 (71)
004 R. Charous	5 (100)	5 (100)	5 (100)
020 R. Hill	5 (100)	5 (100)	4 (80)
005 J. Ervin	2 (100)	2 (100)	2 (100)
021 J. Pappas	2 (100)	2 (100)	0 (0)
<b>Total:</b>	<b>255</b>	<b>253</b>	<b>228</b>

**MO Comment:** The investigators listed above are acceptable. The rates of clinical evaluability for patients were generally similar across centers enrolling greater than 10 patients.

#### 8.3.3.8.2 Demographics

The following table was compiled from the NDA submission (Amendment 15, Volume 1, pg. 58) and the medical officer's analyses of the demographic data sets:

**Demography, All Treated Patients  
Protocol AI420-066**

Characteristic	Number (%) of Patients					
	Gatifloxacin		Trovafloracin		Total	
	ITT N = 122	Eval N=113	ITT N = 131	Eval N=115	ITT N = 253	Eval N=228
<u>Gender</u> [N (%)]						
Male	38(31)	36(32)	49(37)	43(37)	87(34)	79(35)
Female	84(69)	77(68)	82(63)	72(63)	166(66)	149(65)
<u>Race</u> [N (%)]						
White	100(82)	92(81)	102(78)	91(79)	202(80)	183(80)
Hispanic	8(4)	7(6)	14(11)	13(11)	22(9)	20(8)
Black	5(4)	5(4)	10(8)	8(7)	15(6)	13(6)
Other	9(7)	8(7)	5(<1)	1(1)	14(6)	9(4)
<u>Age</u> (years)						
Mean	40	41	43	43	42	42
Median	39	39	43	42	40	41
Min. - Max.	18 - 72	18-72	18 - 75	18-75	18 - 75	18-75
<u>Weight</u> (kg)						
Mean	78	76	82	88	80	81
Median	75	70	80	84	78	74
Min. - Max.	44 - 163	44-163	43 - 158	43-157	43 - 163	43-163

NOTE: Max. = Maximum; Min. = Minimum

MO Comment: Randomization resulted in very comparable baseline demographic characteristics between the treatment groups for both the "All Treated Patients" and "Clinically Evaluable" populations. The enrolled study population was also demographically very similar to that in the other comparator controlled clinical trial, Study AI420-008.

## 8.3.3.8.3 Reasons for Nonevaluability

From the NDA (Amendment 15, Volume 1, pg. 56):

**Distribution of Patients in Study Populations and Reasons for Exclusion**  
**Protocol AI420-066**

Study Population	Number (%) of Patients		
	Gatifloxacin	Trovafloxacin	Total
All Treated	123 (100)	131 (100)	254 (100)
Clinically Evaluable	113 (93)	116 (88)	229 (90)
Unevaluable	9 (7)	16 (12)	25 (10)
<u>Reason Unevaluable</u>			
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)

MO Comment: The medical officer reviewed all patients designated as unevaluable by the sponsor and agreed with all such designations. Note that the above table was modified by the medical officer to correct errors in the database identified by the sponsor in the narrative section of the study report (Amendment 15, Volume 1, page 53). Specifically, patient 008-303 was included in the "All Treated" population, and patient 019-182 was changed to an evaluable treatment failure. For the FDA analysis of the database, the medical reviewer also excluded an additional 10 patients from the evaluable population for the reasons listed below:

Patient ID Number	Drug	Reason for Exclusion
00002 00290	Gatifloxacin	Lacks nasal purulence as per inclusion criteria
00005 00145	Trovafloxacin	"
00006 00235	Gatifloxacin	"
00006 00236	Trovafloxacin	"
00008 00362	Gatifloxacin	"
00014 00114	Gatifloxacin	"
00018 00239	Gatifloxacin	"
00019 00181	Gatifloxacin	"
00001 00397	Gatifloxacin	TOC visit outside time window (day +1)
00023 00208	Trovafloxacin	TOC visit outside time window (day +5)

## 8.3.3.8.4 Prognostic Factors

From the NDA (Amendment 15, Volume 1, pg. 67):

**Prognostic Factors, All Treated Patients  
Protocol A1420-066**

Prognostic Factor	Number (%) of Patients					
	Gatifloxacin		Trovafloracin		Total	
	ITT N = 122	Eval N=113	ITT N = 131	Eval N=115	ITT N = 253	Eval N=228
<u>History of Sinusitis</u>						
Yes	101(83)	97(86)	110(84)	95(83)	211(83)	192(84)
No	21(17)	16(14)	21(16)	20(17)	42(17)	36(16)
<u>Number of Sinusitis Episodes in Past 12 Months</u>						
<3	78(76)	81(72)	92(84)	72(63)	170(80)	153(67)
≥3	24(24)	16(14)	18(16)	23(20)	42(20)	39(17)
Unknown	20	16	21	20	41	36
Median	1	1	1	1	1	1
Minimum – Maximum	0 – 6	0 – 6	0 – 6	0 – 6	0 – 6	0 – 6
<u>Prior Sinus Surgery</u>						
Yes	14(11)	10(9)	13(10)	16(14)	27(11)	26(11)
No		103(91)	118(90)	99(86)	226(89)	202(89)
		108(89)				
<u>Allergic Rhinitis</u>						
Yes	92(75)	83(73)	94(72)	79(69)	186(74)	162(71)
No	30(25)	30(27)	37(28)	36(31)	67(26)	66(29)
<u>Bilateral Infection</u>						
Yes	59(48)	59(52)	64(49)	57(50)	123(49)	116(51)
No	63(52)	54(48)	67(51)	58(50)	130(51)	112(49)

MO Comment: The percentage of patients having three or more sinus infections within the previous year was slightly higher in the trovafloracin group when compared to the gatifloxacin group. The two treatment arms were otherwise balanced with respect to the above prognostic factors listed by the sponsor. As previously noted, allergic rhinitis and prior sinus pathology are recognized prognostic factors, the but the importance of bilaterality of infection is unclear.

## 8.3.3.8.5 Pre-treatment Signs/Symptoms

The following table compiles data from the study report (Amendment 10, Volume 1, page 63) and the medical officer analysis of the data sets for the clinically evaluable population:

**Primary Pre-treatment Signs and Symptoms of Acute  
Maxillary Sinusitis, All Treated Patients  
Protocol AI420-066**

Sign/Symptom <sup>a</sup>	Number (%) of Patients					
	Gatifloxacin		Trovafloracin		Total	
	ITT N = 122	Eval N=113	ITT N = 131	Eval N=115	ITT N = 253	Eval N=228
Congestion, Nasal	114(93)	107(95)	126(96)	111(97)	240(95)	218(96)
Discharge, (Nasal, Purulent	113(93)	106(94)	126(96)	112(97)	239(94)	218(96)
Tenderness, Sinus	112(92)	106(94)	114(87)	100(87)	226(89)	206(90)
Pressure, Face	108(89)	103(91)	110(84)	96(83)	218(86)	199(87)
Pain, Sinus	106(87)	100(88)	110(84)	96(83)	216(85)	196(86)
Postnasal Drip	101(83)	95(84)	112(85)	99(86)	213(84)	194(85)
Pain, Face	98(80)	94(83)	103(79)	92(80)	201(79)	186(82)
Headache	98(80)	92(81)	103(79)	89(77)	201(79)	181(79)
Coughing	87(71)	80(71)	101(77)	92(80)	188(74)	172(75)
Malaise	73(60)	68(60)	84(64)	74(64)	157(62)	142(62)
Sore Throat	65(53)	61(54)	64(50)	58(50)	129(51)	119(52)
Swollen Sinus	60(49)	56(50)	68(52)	58(50)	128(51)	114(50)
Discharge, Nasal, Watery	58(48)	52(46)	68(52)	64(56)	126(50)	116(51)
Hyposmia	58(48)	54(48)	62(47)	56(49)	120(47)	110(48)
Pain, Dental	38(31)	37(33)	52(40)	47(41)	90(36)	84(37)
Halitosis	41(34)	39(35)	45(34)	40(35)	86(34)	79(35)
Chills	30(25)	29(26)	34(26)	31(27)	64(25)	60(26)
Fever (>38°C/100.4°F)	8(7)	7(6)	13(10)	11(10)	21(8)	17(7)

<sup>a</sup> Patients may be included in more than one category

**MO Comment: The two treatment groups were similar in their baseline signs and symptoms of the acute infection. While nasal purulent discharge (from the nose, in the throat, or at the "maxillary orifice") was an inclusion criterion, not all subjects enrolled met this criterion as shown in the table**

above and were excluded in the FDA analysis of the clinically evaluable population (see *Reasons for Nonevaluability* subsection above). The reviewer verified that all patients enrolled had the protocol-required symptom of sinus pain and/or pressure.

#### 8.3.3.8.6 Reasons for Discontinuation

From the NDA (Amendment 15, Volume 1, pg. 71):

#### Reasons for Discontinuation of Study Medication, All Treated Patients Protocol AI420-066

Reason Discontinued	Number (%) of Patients		
	Gatifloxacin N = 122	Trovafloxacin N = 131	Total N = 253
Number Completed Therapy	111 (91)	114 (87)	225 (89)
<u>Number Discontinued Prematurely</u>	11 (9)	17 (13)	28 (11)
Adverse Clinical Event	8 (7)	16 (12)	24 (9)
Other	2 (2)	1 (<1)	3 (1)
Laboratory Test Abnormality	1 (<1)	0	1 (<1)

MO Comment: Premature discontinuations of therapy were slightly more frequent in the trovafloxacin group mainly reflecting the greater incidence of adverse events (see *Safety* section) below. One gatifloxacin patient with abnormal baseline liver function tests was discontinued from the study.

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## 8.3.3.8.7 Study Drug Exposure

Study Medication Usage, All Treated Patients  
Protocol A1420-066

Extent of Dosing	Number (%) of Patients		
	Gatifloxacin N = 122	Trovafloracin N = 131	Total N = 253
<u>Number of doses</u>			
1	1 (<1)	6 (5)	7 (3)
2 - 7	6 (5)	10 (8)	16 (6)
8 - 9	7 (6)	5 (4)	12 (5)
10	108 (89)	110 (84)	218 (86)
<u>Duration (days)</u>			
Mean	10	9	9
Median	10	10	10
Minimum - Maximum	1 - 11	1 - 10	1 - 11
<5	6 (5)	12 (9)	18 (7)
5-7	1 (1)	4 (3)	5 (2)
8-10	114 (93)	115 (88)	229 (91)
>10	1 (1)	0	1 (<1)

MO Comment: A slightly higher percentage of gatifloxacin-treated patients completed a full 10-day course of therapy compared to the trovafloracin (89% vs. 84%), due mainly to the higher rate of dropouts due to adverse clinical events in the latter group.

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## 8.3.3.8.8 Efficacy

Primary Efficacy Analysis

The clinical efficacy results analysis, as per the sponsor and the FDA medical reviewer, are shown below for both the "All Treated Patients" and "Clinically Evaluable" populations at the Test of Cure Visit (+7 to +14 days following completion of study drug therapy):

**Clinical Response, All Treated Patients**  
**Protocol AI420-066**

Clinical Response	Number (%) of Patients					
	Gatifloxacin		Trovafloracin		Total	
	BMS N = 123	FDA N = 123	BMS N = 131	FDA N = 131	BMS N = 254	FDA N = 254
Cured <sup>a,b</sup>	99(80)	99(80)	100(76)	98(75)	199(78)	197(78)
Failure	14(11)	14(11)	16(12)	18(14)	29(11)	32(13)
Unable to Determine	10(8)	10(8)	15(11)	15(11)	25(10)	25(10)

<sup>a</sup> 95% Confidence interval for the difference in Cure rate: (-7.2, 16.1) for BMS population

<sup>b</sup> 95% Confidence interval for the difference in Cure rate: (-5.8, 17.7) for FDA population

**MO Comment:** As noted in the study report, Patient 008-003 was excluded from the All Treated Patients population in error. The BMS clinical response rates above were corrected by the MO from the sponsor's original table in the NDA submission (Amendment 15, Volume 1, p. 53). Both BMS and FDA analyses demonstrate slightly higher cure rates in the gatifloxacin arm.

**Clinical Response, Clinically Evaluable Patients**  
**Protocol AI420-066**

Clinical Response	Number (%) of Patients					
	Gatifloxacin		Trovafloracin		Total	
	BMS N = 113	FDA N = 107	BMS N = 116	FDA N = 112	BMS N = 229	FDA N = 219
Cured <sup>a,b</sup>	99(88)	94(88)	100(87)	94(84)	199(87)	188(86)
Failure	14(12)	13(12)	16(13)	18(16)	29(13)	31(14)

<sup>a</sup> 95% Confidence interval for the difference in Cure rate: (-9.6, 12.2) for BMS evaluable population

<sup>b</sup> 95% Confidence interval for the difference in Cure rate: (-7.0, 15.8) for FDA evaluable population

**MO Comment:** The cure rates for the clinically evaluable patient populations are acceptable. The response rates and confidence intervals for both the sponsor and the FDA analyses meet the protocol-defined criteria for clinical equivalence.

**Clinical Response at Extended Follow-Up**

Clinical response, as assessed by telephone query, was available for 224/228 (98%) of the sponsor's clinically evaluable patients at +21 to +28 days following therapy as shown in the following table from the NDA (Amendment 15, Volume 1, pg. 85):

**Clinical Response at Extended Follow-Up, Clinically Evaluable Patients  
Protocol AI420-066**

Clinical Response	Number (%) of Patients		
	Gatifloxacin N = 110	Trovafloracin N = 114	Total N = 224
Cured <sup>a</sup>	92 (84)	94 (82)	186 (83)
Failure	18 (16)	20 (18)	38 (17)

a. 95% Confidence interval for the difference in Cure rate: (-10.1, 13.5)

**MO Comment:** Based on followup data in a very high percentage of the sponsor's clinically evaluable population, the cure rates for both treatment arms were sustained from the test of cure visit and remained comparable to each other.

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### 8.3.3.8.9 Safety

#### Deaths

No patients died during the study.

#### Serious Adverse Events

Two serious adverse clinical events occurred during the study, neither of which was considered by the investigators to be drug-related:

Study Drug	Patient No.	Study Day	Event
Gatifloxacin	018-172	+18	Exacerbation of bipolar disorder
Trovafloracin	009-281	5	Exacerbation of COPD

#### All Adverse Clinical Events

During the study, 199 patients (79%) experienced one or more adverse clinical events. The trovafloracin group experienced a greater frequency of adverse events compared to the gatifloxacin group (81% vs. 76%, respectively). The most common adverse clinical events across both treatment groups were nausea (30% in each arm), rhinitis (30% gatifloxacin, 22% trovafloracin), dizziness (29% gatifloxacin, 56% trovafloracin), insomnia (20% gatifloxacin, 23% trovafloracin), and headache (15% gatifloxacin, 20% trovafloracin).

For a complete listing of adverse events, refer to the NDA submission (Amendment 15, Volume 1, pg. 90).

#### Drug Related Adverse Events

The table on the following page was modified from the original table in the NDA submission (Amendment 15, Volume 1, pg. 95) to show only drug-related adverse events by severity which occurred with a greater than or equal to 1% frequency in the gatifloxacin treatment group.

**MO Comment:** Drug-related adverse events were more commonly seen in this study (66% of patients) compared to the A1420-008 (45% of patients). Gastrointestinal symptoms of mild severity were again the most common overall. Dizziness was commonly seen in trovafloracin treated patients (53%), consistent with the product labeling. Interestingly, dizziness was also reported in 26% of gatifloxacin-treated patients in this study compared

to <1 % of patients in the AI420-008 study and only 3% in the AI420-007 study. The discrepancy may be due to differences in study sites, study populations, or (most likely) a heightened awareness of this symptom due to its frequency in the trovafloxacin arm. Other adverse clinical events associated with the fluoroquinolone class were uncommon in the present study. No hepatotoxicity, phototoxic skin reactions, tendonopathy, or cardiac problems were reported.

Only 8 of the 24 discontinuations from the study due to adverse events occurred in gatifloxacin treated patients. Of these 8 patients, the medical officer felt that 1 patient was misclassified: patient AI420-066-009-161 was actually a treatment failure who withdrew due to worsening symptoms and received alternative antimicrobial therapy. Patient AI420-066-0002-197 withdrew due to chlamydia exposure (i.e., not study-related). The remaining 6 patients withdrew due to adverse events which were judged to be related to gatifloxacin therapy: 4 patients with nausea and/or vomiting, 1 patient with vaginal moniliasis and vague arm/leg pain, and 1 patient with hives, itching and tachycardia following one day of therapy. The latter patient raises concern regarding a possible Type I immediate hypersensitivity reaction, similar to the patients described in the medical officer safety review for protocols AI420-008 and AI420-007 above. Review of post-marketing adverse events should include a heightened awareness of this concern.

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**Drug-Related Adverse Clinical Events, by Severity; All Treated Patients  
Protocol AI420-066**

Adverse Clinical Event	Number (%) of Patients									
	Gatifloxacin (N = 122)					Trovafloracin (N = 131)				
	Mild	Moderate	Severe	Not Recorded	Total	Mild	Moderate	Severe	Not Recorded	Total
<b><u>Any Drug-Related Adverse Clinical Event</u></b>	41 (34)	19 (16)	5 (4)	0	65 (53)	49 (37)	32 (24)	5 (4)	0	86 (66)
Nausea	25 (20)	9 (7)	1 (<1)	0	35 (29)	19 (15)	15 (11)	1 (<1)	0	35 (27)
Dizziness	24 (20)	6 (5)	1 (<1)	1 (<1)	32 (26)	49 (37)	17 (13)	3 (2)	0	69 (53)
Insomnia	12 (10)	4 (3)	0	0	16 (13)	15 (11)	3 (2)	0	0	18 (14)
Moniliasis Vaginal <sup>a</sup>	4 (5)	6 (7)	0	0	10 (12)	2 (2)	1 (1)	0	0	3 (4)
Headache	5 (4)	2 (2)	1 (<1)	0	8 (7)	7 (5)	7 (5)	1 (<1)	0	15 (11)
Diarrhea	4 (3)	2 (2)	0	0	6 (5)	2 (2)	1 (<1)	1 (<1)	0	4 (3)
Dry Mouth	2 (2)	1 (<1)	0	0	3 (2)	3 (2)	0	0	0	3 (2)
Nervousness	2 (2)	0	0	0	2 (2)	0	1 (<1)	0	0	1 (<1)
Pain	0	1 (<1)	1 (<1)	0	2 (2)	0	1 (<1)	0	0	1 (<1)
Pain Abdomen	2 (2)	0	0	0	2 (2)	1 (<1)	0	0	0	1 (<1)
Vomiting	2 (2)	1 (<1)	0	0	3 (2)	0	4 (3)	0	0	4 (3)

<sup>a</sup>Percentages are based on the number of females in the respective treatment group

### Clinical Laboratory Evaluation

Only one patient (in the gatifloxacin arm) discontinued the study due to laboratory abnormalities. Her baseline labs revealed elevated liver function test results that improved on follow-up testing. In patients with normal baseline laboratory values, the development of abnormal values was uncommon and was generally mild (grade 1) when it occurred (see NDA Amendment 15, Volume 1, page 102). Two patients in each treatment arm developed Grade 2 elevations in bilirubin, while one patient in each treatment arm developed Grade 3 decreases in neutrophil counts; there were no additional follow-up values available for these patients in the NDA. There were no Grade 4 abnormalities documented in this study. Worsening of abnormal baseline laboratory values was very uncommon. One patient in each arm worsened to a grade 3 liver function test abnormality. Two other gatifloxacin patients worsened to Grade 3 abnormalities for amylase and glucose (a known diabetic patient).

**MO Comment:** Clinically relevant lab abnormalities as defined by the sponsor (Grade 3 or 4) were very uncommon in both treatment arms. As noted above, the sponsor will submit an overall review of the serum glucose data which will be reviewed in the overall Integrated Safety Summary for the NDA (per Dr. Korvick).

#### 8.3.3.9 Medical Officer's Summary/Conclusions

This randomized, double-blinded was submitted to FDA in June, 1999 as a major amendment to the original NDA. The active control in this trial, trovafloxacin, was an appropriate, FDA-approved comparator agent for acute sinusitis trials while this study was being conducted. However, post-marketing experience with trovafloxacin has revealed its potential to cause serious liver injury and recently revised labeling restricts its usage to serious life- or limb-threatening infections. The safety and efficacy data obtained from this study is nonetheless valid in supporting the NDA.

The design of this study was very similar to that of the other comparative trial for this indication, Study AI420-008 with one major exception: the test of cure visit occurred at +7 to +14 days following completion of therapy (as opposed to a Day +19 to +30 day window in Study AI420-008). The study enrolled a total of 255 patients across the United States, of whom 229 were considered clinically evaluable by the sponsor (113 gatifloxacin patients, 116 trovafloxacin patients). The sponsor's response rate at the test of cure visit for these clinically evaluable patients was 88% and 87% for the gatifloxacin and trovafloxacin arms, respectively. The 95% C.I. for the difference in efficacy rates was (-9.2, 12.2).

For the All-Treated Patients population, the sponsor's response rates were 80% and 76% for gatifloxacin and trovafloxacin, respectively, 95% C.I.= (-7.2,16.1).

The FDA medical officer's review of the clinical efficacy data disqualified an additional ten patients from the clinically evaluable patient population. The FDA clinical response rates for the evaluable patient population at the test of cure visit were 88% and 84%, for the gatifloxacin and trovafloxacin arms, respectively, 95% C.I. = (-7.0, 15.8). For the All-Treated Patients population, the FDA response rates were 80% and 75%, 95% C.I. = (-5.8, 17.7). Thus, the FDA analysis resulted in an even more favorable response rate of gatifloxacin compared to trovafloxacin.

The safety data from this trial again reveal that gastrointestinal symptoms (nausea, diarrhea, abdominal pain, vomiting) were the most common drug-related adverse events associated with gatifloxacin therapy. Dizziness was reported much more frequently in this study (26% of patients) compared to the other two studies in the NDA. This may be due, in part, to the very high frequency of dizziness in the trovafloxacin arm (53% of patients), leading to an increased investigator's attention toward this event. One gatifloxacin patient developed hives, tachycardia, and itching demonstrating the potential for Type I immediate hypersensitivity reactions seen in the other two studies. Clinically relevant lab abnormalities were uncommon in both treatment arms.

In conclusion, gatifloxacin the efficacy data from this trial demonstrates the equivalence of gatifloxacin to the (formerly) approved comparator, trovafloxacin as defined by the protocol-specified criteria. The safety profile of gatifloxacin in this trial was acceptable. This study supports approval of gatifloxacin for the acute sinusitis indication.

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cc: NDA 21-061  
HFD-590  
HFD-590/MO/Korvick  
HFD-590/DepDir/Albrecht  
HFD-520/Pharm/Ellis  
HFD-520/Micro/Altaie  
HFD-590/Chem/  
HFD-590/CSO/Atkins  
Clinical Review GC

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## APPENDIX I

### FDA- Approved Antimicrobial Agents for Sinusitis

#### 1. CEFTIN

CEFTIN Tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute Bacterial Maxillary Sinusitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase-producing strains only). (See CLINICAL STUDIES section.)

NOTE: In view of the insufficient numbers of isolates of beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* that were obtained from clinical trials with CEFTIN Tablets for patients with acute bacterial maxillary sinusitis, it was not possible to adequately evaluate the effectiveness of CEFTIN Tablets for sinus infections known, suspected, or considered potentially to be caused by beta-lactamase-producing *Haemophilus influenzae* or *Moraxella catarrhalis*.

#### 2. AUGMENTIN

Augmentin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Sinusitis –caused by (beta)-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

#### 3. OMNICEF

OMNICEF (cefdinir) Capsules and OMNICEF (cefdinir) for Oral Suspension are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Acute Maxillary Sinusitis caused by *Haemophilus influenzae* (including (beta)-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including (beta)-lactamase producing strains).

#### 4. LEVAQUIN

LEVAQUIN Tablets are indicated for the treatment of adults ( $\geq 18$  years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute maxillary sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

#### 5. LORABID

Lorabid is indicated in the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see DOSAGE AND ADMINISTRATION for specific recommendations.)

Acute Maxillary Sinusitis \*\*\* caused by *S. pneumoniae*, *H. influenzae* (non-(beta)-lactamase-producing strains only), or *M. catarrhalis* (including (beta)-lactamase-producing strains). Data are insufficient at this

time to establish efficacy in patients with acute maxillary sinusitis caused by (beta)-lactamase-producing strains of *H. influenzae*.

\*\*/\* NOTE: In a patient population with significant numbers of (beta)-lactamase-producing organisms, loracarbef's clinical cure and bacteriological eradication rates were somewhat less than those observed with a product containing a (beta)-lactamase inhibitor. Lorabid's decreased potential for toxicity compared to products containing (beta)-lactamase inhibitors along with the susceptibility patterns of the common microbes in a given geographic area should be taken into account when considering the use of an antimicrobial ( see CLINICAL STUDIES section). For information on use in pediatric patients, see PRECAUTIONS--Pediatric Use.

#### 6. CEFZIL

CEFZIL (cefprozil) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute Sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including (beta)-lactamase-producing strains) and *Moraxella (Branhamella) catarrhalis* (including (beta)-lactamase-producing strains).

#### 7. CIPRO

CIPRO® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Acute Sinusitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*

#### 8. BLAXIN

BLAXIN Filmtab tablets and BLAXIN Granules for oral suspension are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

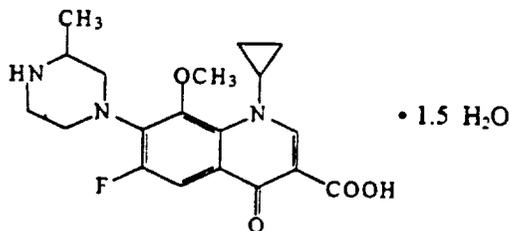
Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

## 8.4 Medical Officer Review of NDA 21-061: Gatifloxacin (Tequin <sup>TM</sup>) for the treatment of uncomplicated skin and skin structure infections

Date Submitted: 28 December 1998  
Date Received: 29 December 1998  
Date Assigned: 29 December 1998  
Date Completed: 22 October 1999

Applicant: Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, Connecticut 06492  
203-677-6883  
Contact person: Douglas Kriesel, Ph.D.

Drug: Proprietary name - Tequin <sup>TM</sup>  
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  
Molecular formula - C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> • 1.5 H<sub>2</sub>O  
Molecular weight - 402.42 (sesquihydrate)  
Molecular structure -

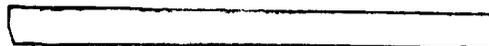


Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets

Related NDA: 21-062



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### Executive Summary

Bristol-Myers Squibb has submitted NDA 21-061 for seven indications. One of the indications, and the subject of this review, is for the treatment of uncomplicated skin and skin structure infections. The proposed dosage is 400 mg per day, orally, for 7 to 10 days; following is the indication as it appears in the proposed label:

“Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*,  $\beta$ -hemolytic streptococci (including *Streptococcus pyogenes*, and *Streptococcus agalactiae*), or *Acinetobacter* spp.”

Appendix A contains a list of the products currently approved for this indication in the United States. Currently, the quinolone antimicrobials that are approved for the treatment of uncomplicated skin and skin structure infections are:

1. Levofloxacin: caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.
2. Ofloxacin: caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Proteus mirabilis*.
3. Ciprofloxacin: caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, (methicillin susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

(Note: Ciprofloxacin's label has a table listing dosages guidelines per indication and it has an entry under Skin and Skin Structure for “Severe/Complicated.” It is believed that the use of the term “complicated” in this label is different than how it is presently intended in the Points to Consider document, as it precedes the existence of the document.)

The clinical data in the applicant's NDA submission for this indication were derived from one trial. It was a multicenter, randomized, double-blind, active-control trial. There were 31 centers recruited, of which 27 were able to enroll patients. A table listing of the centers involved is provided in Appendix B. The table below outlines the design of the study trial.

Study Number	Study Design	Start - Completion Dates	Number of Subjects	Age Range	Dose	Duration of Treatment
A1420-005	Randomized, double-blind, multi-center, Phase II/III study	29 August 1997 – 11 May 1998	410 enrolled; 407 received at least one dose of therapy	18-90 years	Daily doses of either 400 mg of gatifloxacin, or 500 mg of levofloxacin.	7 to 10 days

In the clinically evaluable population, the applicant reported a clinical response rate that was equivalent to the comparator:

**Clinical Response at Test of Cure Visit, Clinically Evaluable Patients**

Clinical Response	Number of Patients (%)		
	Gatifloxacin N = 161	Levofloxacin N = 172	Total N = 333
Cure	146 (91)	145 (84)	291 (87)
Failure	15 (9)	27 (16)	42 (13)

95% Confidence Interval for Difference in Cure Rate: (-2.0 , 15.2 )

Additional analyses by Dr. Silliman to assess the strength of the data included evaluation of the clinical response rates based on the patient subpopulations:

**Clinical Cure Rates by Analysis Population**

Analysis Population	Number Cured/Number of Patients (%)		
	Gatifloxacin N = 205	Levofloxacin N = 205	95% Confidence Interval*
All Treated Patients	162/202 (80)	161/205 (79)	(-6.9%, 10.9%)
Clinically Eligible Patients	159/193 (82)	159/199 (80)	(-6.1%, 11.6%)
Clinically Evaluable Patients	146/161 (91)	145/172 (84)	(-2.0%, 15.2%)
Microbiologically Evaluable Patients	88/95 (93)	75/85 (88)	(-6.5%, 16.8%)

\*For the difference in cure rates, gatifloxacin minus levofloxacin.

***Special populations***

Gatifloxacin's efficacy rates were similar to levofloxacin in the subset categories of gender, age, and ethnic group.

Gatifloxacin adverse event rates were similar to levofloxacin in the subset categories of age and ethnic groups. There were more serious adverse events reported in the gatifloxacin treatment group than in the levofloxacin treatment group. However, these were not significantly different with respect to age, gender, or ethnic group within the gatifloxacin treatment group.

It was noted that overall, more adverse events were reported for female patients than for male patients in the gatifloxacin treatment group (156 to 75). Although this trend was also observed in the levofloxacin treatment group (142 to 102 events), it was numerically higher in the gatifloxacin treatment group.

"Nausea" was the only adverse event that was reported in females more than in males – out of 17 patients, 14 were females. Most were graded as "Mild/Grade 1" in severity. This was similar to the levofloxacin treatment group with respect to severity, however the gender breakdown was slightly different in the levofloxacin treatment group – out of 17 patients, 11 were females. It is believed that these numbers are too small to be able to draw any significant conclusions about this finding, other than the fact that it was observed.

The incidences of abnormal laboratory values were similar within the subset categories of age, gender, and ethnic group.

**Recommendation**

The Food and Drug Administration (FDA) Points to Consider document from the Division of Anti-Infective Drug Products (October 1992), indicates that in order for this general claim to be granted, there should be at least 20% each of the following: simple abscesses, impetiginous lesions, furuncles, and cellulitis. The applicant was able to study sufficient number of patients for three of the four types of infections. They were not able to study sufficient number of patients with impetiginous lesions.

The medical officer recommendation for gatifloxacin regarding uncomplicated skin and skin structure infections :

1. Approval of the indication only for methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pyogenes*.
2. The label should reflect the type of uncomplicated skin infections that were studied in this clinical trial; a) simple abscesses, b) furuncles, c) folliculitis, d) wound infections, and e) cellulitis.
3. The label should indicate that an insufficient number of patients with the diagnosis of impetiginous lesions were available for evaluation.

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**Review Team**

<i>Regulatory Management Officer:</i>	Brenda Atkins, B.S.
<i>Chemistry Reviewer:</i>	John Smith, Ph.D.
<i>Microbiology Reviewer:</i>	Sousan Altaie, Ph.D.
<i>Pharmacokinetics/Biopharmaceutics Reviewer:</i>	Kathleen Uhl, Ph.D.
<i>Pharmacotoxicologist Reviewer:</i>	Amy Ellis, Ph.D.
<i>Biometrics Reviewer:</i>	Nancy Silliman, Ph.D.
<i>Medical</i>	
<i>Medical Reviewer:</i>	R. Roca, M.D.
<i>Lead Medical Reviewer:</i>	J. Korvick, M.D., M.P.H.
<i>Medical Team Leader:</i>	M. Cavallé-Coll, M.D., Ph. D.

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## 8.4.1 Study No. A1420-005 – A Randomized, Double-Blind, Multicenter, Comparative Study of Gatifloxacin vs. Levofloxacin in the Treatment of Uncomplicated Skin and Soft Tissue Infections

### 8.4.1.1 Efficacy Evaluation

#### 8.4.1.1.1 Study Design and Objectives

The study was a randomized, double-blind, multicenter study. Twenty-seven centers were recruited, and 410 patients were enrolled. Patients were randomized to gatifloxacin, 400 mg daily, or levofloxacin, 500 mg daily. Duration of treatment was 7 to 10 days.

There were three objectives in this study:

1. Assess the efficacy of gatifloxacin in the treatment of uncomplicated skin and soft tissue infections, as compared to levofloxacin.
2. Assess the safety relative to a standard regimen of levofloxacin.
3. Demonstrate microbiological eradication rates and responses for the most common pathogens causing skin infections.

#### Reviewer's Comment

*The product insert for levofloxacin (Levaquin ®) includes the following:*

*"Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due Staphylococcus aureus, or Streptococcus pyogenes." Therefore, levofloxacin is an appropriate comparator for this trial.*

#### 8.4.1.1.2 Eligibility Criteria

##### *Inclusion Criteria*

Male and female patients were eligible if they were older than 18 years of age, and able to give informed consent (or have a legally authorized representative available). Female patients were to have a negative pregnancy within 72 hours prior to initiating therapy and effective birth control while on study. Patients were to have at least one of the following skin/soft tissue infections:

- a **impetigo**: identified by honey-colored crusts, or thin, varnish-like crust
- b **erysipelas or cellulitis**: identified by erythema in association with at least one of the following: *pain, tenderness, warmth, edema, induration, fever*
- c **folliculitis**: identified by erythematous papules, with or without central pustules, and occurring in the region of hair follicles
- d **wound infections**: the infected wound could be a surgical incision, bite (human or animal), other puncture wound, abrasion, or laceration with erythema, and at least one of the following: *pain, tenderness, warmth, serous or purulent drainage*
- e **abscess(es)**: identified by the formation of a subcutaneous nodule(s), with or without erythema, tenderness, fluctuance, or purulent drainage

**Exclusion Criteria**

Patients would be ineligible if they met any of the following criteria at the time of randomization:

- a. Complicated infections, such as:
  - Burn wounds
  - Diabetic foot ulcers
  - Gangrene
  - Decubitus ulcers
  - Ecthyma gangrenosum
  - Infection of prosthetic material
  - Necrotizing fasciitis
  - Secondary infection of a chronic skin disease
- b. Immediate need for surgical intervention
- c. Infection that could be treated by surgical incision alone
- d. Known or suspected fungal, parasitic or viral infection
- e. Concomitant topical treatment with antimicrobial or corticosteroids
- f. Concomitant osteomyelitis or other bacterial infection
- g. Deep venous thrombosis
- h. Need for longer than ten days of antibacterial therapy, or the need for hospitalization for intravenous therapy
- i. Receipt of systemic antibiotic therapy within the seven days period prior to randomization, or likelihood of receiving other antibiotics during participation in the study
- j. Previously diagnosed disease(s) of immune function
- k. Pregnancy or lactation
- l. Malabsorption syndromes or other gastrointestinal conditions affecting drug absorption
- m. History of significant hypersensitivity reaction to flouoroquinolones
- n. Known renal insufficiency
- o. Current clinically significant hepatic disease
- p. Previous enrollment in any gatifloxacin study

**Reviewer's Comments**

*Eighteen patients had deviations from the enrollment criteria. They are summarized below, in a table adapted from a table in the applicant's Study Report (Table 7.3, p. 55):*

**Protocol Violations of Enrollment Criteria, All Treated Patients**

Violation	Number of Patients		
	Gatifloxacin N = 202	Levofloxacin N = 205	Total N = 407
Pre-treatment antibiotic	2	4	6
Surgical intervention	3	2	5
Missing required symptom(s) at entry	2	2	4
Superinfection of underlying disease	1	2	3
<b>TOTAL</b>	<b>8</b>	<b>10</b>	<b>18</b>

*None of these patients were considered clinically evaluable, and therefore not included by the applicant in the efficacy analyses. It is noted that the number of protocol violations was comparable between the treatment arms.*

*In addition, the clinical investigator inspections by the Division of Scientific Investigations (DSI), HFD-47, identified two additional patients that had been enrolled in the study despite not being eligible per protocol exclusion criteria. Neither of these two patients had been identified as ineligible in the database provided by the applicant.*

*The first patient, #022-00131 (Gatifloxacin treatment arm), had received antibiotic therapy within the seven days prior to randomization. Review of the case report form revealed that although inclusion of the patient in the study was a violation of the inclusion/exclusion criteria, the last dose of the antibiotic therapy had occurred six days prior to study initiation. Furthermore, the clinical presentation at the time of randomization made it reasonable to include the patient in the study.*

*The second patient, #022-00521, had been admitted in to the study, even though the diagnosis was burn wound infection. Although this was a violation of the inclusion/exclusion criteria, the patient was not included in any of the efficacy analyses because the patient had been deemed to be clinically unevaluable. The patient received levofloxacin for a sinus infection prior to the Test of Cure Visit; therefore it was not possible to assess a clinical response.*

*It is believed that these two discrepancies in the applicant's database that were identified by DSI did not have a significant impact on the overall results of the study.*

#### 8.4.1.1.3 Study Drugs and Randomization Methods

The randomization of patients to a treatment arm was performed using a dynamic balancing algorithm. The rationale was that this would minimize any imbalance of treatment arms within each site, each level of diagnosis, and for the overall study.

The blinding method included a double-dummy, double-blind technique. Each patient was supplied with a blister card that contained enough study drug for ten days of therapy. The blister card contained 10 capsules of 400 mg gatifloxacin or its matching placebo, as well as 20 capsules of 250 mg levofloxacin or its matching placebo.

#### Reviewer's Comments

*Please refer to Dr. Nancy Silliman's review for details about the implications of this method. In brief, Dr. Silliman notes this randomization method could be useful when there are large number of covariates that are to be balanced at the randomizaion stage. However, Dr. Silliman notes that there is currently no*

*known way to extend this type of analysis to an active-controlled trial with binary outcome data.*

*Dr. Silliman felt that the results from this trial would need to be viewed in a conservative light, because the actual Type I error associated with the 95% confidence interval is unknown. With this in mind, she performed additional analyses, including one where missing gatifloxacin values were imputed to be failures and missing levofloxacin values were imputed to be successes. In this analysis, both lower bounds remained above -15%, whereupon it was Dr. Silliman's conclusion that the randomization strategy used did not have a significant impact on the results of the study.*

#### 8.4.1.1.4 Study Endpoints

Clinical and bacteriological endpoints were to be evaluated at the Day +7 to Day +14 post-treatment visit, also called the "Test of Cure Visit." This visit could occur from Day +5 to Day +18, in order to allow for individual scheduling issues. If there were multiple visits within this window, the last visit was utilized.

The clinical response was assigned according to the following defined criteria:

- **Cure**
  - All signs and symptoms related to the infection were resolved, or improved to the point that no further antimicrobial therapy was indicated.
- **Failure**
  - Persistent, worsening, or new signs and symptoms of skin and soft tissue infection.
  - Surgery was required of the affected area after therapy had begun.
- **Unable to determine**
  - No Test of Cure Visit was performed.
  - Patient received another antibiotic with documented activity against the pathogen for an infection other than the infection that permitted enrollment in the study, prior to the Test of Cure Visit.

#### Reviewer's Comment

*The applicant provided a list of patients where there were discrepancies between the investigator's and the applicant's assessment of clinical response. In the gatifloxacin treatment group, there were 3 patients whose response was changed from "failure" to "cured," and 1 where it was changed from "cured" to "failure." In the levofloxacin treatment group, there were 4 patients whose response was changed from "cured" to failure."*

*Although these reassignments would seem to favor the gatifloxacin treatment arm, review of the case report forms revealed no reason to reject the applicant's re-assignment of the gatifloxacin patients. Of the four levofloxacin patients that were re-assigned by the applicant, one was not included in any of the efficacy evaluations (Patient #030 00242), and the re-assignment for two of the patients was deemed to be reasonable by this reviewer. This reviewer assessed that the*

*fourth patient should have remained a "cured" (Patient #023 00046), however, it is believed that this reassignment by the applicant did not have a significant impact on the overall efficacy results of the study.*

The bacteriological response was assigned according to the following defined criteria:

- **Eradication**

*Documented:* No growth of the pre-treatment pathogen on a post-therapy culture. Further, there was no growth of a new potential pathogen on the post-therapy culture.

*Presumed:* A post-therapy culture was not obtained because there was no culturable material. There must have been an adequate clinical response.

- **Persistence**

– *Documented:* continued presence of the pre-treatment pathogen in the culture.

– *Presumed:* No appropriate site to culture, but the clinical response was a failure.

- **Unable to Determine**

– The pathogen was resistant to therapy.

– Unable to determine the clinical response.

– The patient received another systemic antibiotic that was presumably effective, for an infection other than a skin or soft tissue infection, prior to obtaining a culture specimen.

In addition, patients with "new infections" were identified as those patients who had any of the following at any time during, or after study drug therapy:

1. isolation of a new pathogen from the culture of a lesion specimen, with concurrent signs and symptoms of infection
2. isolation of any pathogen from a new site of infection, with concurrent signs and symptoms of infection
3. clinical signs and symptoms consistent with a new infection

Reviewer's Comments

*In order to test the robustness of the efficacy results, Dr. Silliman performed a conservative analysis. Missing values in the gatifloxacin treatment group (those classified as "unable to determine") were considered failures, and missing levofloxacin values in the levofloxacin treatment group were considered successes. This is discussed further in her review, but it was noted that in that analysis, gatifloxacin still had a favorable response rate when compared to levofloxacin.*

Safety assessment included evaluation for adverse events up to thirty days after therapy with study drug had terminated.

#### 8.4.1.1.5 Termination and Clinical Follow-up

The protocol stipulated that patients would be discontinued for any of the following reasons:

- Adverse events
- Intercurrent illnesses
- Persistence or worsening of signs and symptoms of acute infection after 3 days of study drug therapy
- If the investigator felt it in the patient's best interest
- The patient became pregnant
- The patient wished to withdraw

Patients were followed for thirty days after the termination of study drug therapy. If the patient discontinued because of an adverse clinical event, they were followed to document that the reaction had subsided and no complications persisted.

#### Reviewer's Comments

*There were 13 patients (3 %) who discontinued therapy and were lost to follow-up in the study. Two of them were in the levofloxacin treatment group, and 11 in the gatifloxacin treatment group. The applicant did not advance any explanation as to the reason for this imbalance in follow-up between the two treatment groups.*

#### 8.4.1.1.6 Sample Size and Statistical Plan

The study was based on the assumption that levofloxacin had a clinical response rate of 80% in patients with uncomplicated skin and skin structure infections. The applicant's hypothesis was that gatifloxacin would have an equivalent rate, and estimated that 150 evaluable patients per treatment arm would have 90% power to detect a 15% difference between the two treatment arms. The applicant therefore targeted the study for 190/treatment arm (380 total patients), to incorporate an 80% evaluability rate.

In addition, patients were stratified by diagnosis (impetigo, cellulitis/erysipelas, wound, or abscess/folliculitis), and the applicant attempted to enroll at least 30 patients/diagnosis in each treatment arm.

The applicant indicated that patients were analyzed "as treated" which meant inclusion in the treatment group according to actual treatment received. In addition, there were four patient populations that were identified for analyses by the applicant:

- **All Treated Patients** – all randomized patients who received at least one dose of study drug.
- **Clinically Eligible Patients** – all treated patients who had at least one of the following infections:
  - Impetigo
  - Cellulitis
  - Wound infection
  - Erysipelas
  - Folliculitis
  - Abscess(es)

- **Clinically Evaluable Patients** – all clinically eligible patients who met *all* of the following conditions:
  - received at least five days of treatment with study drug
  - had a pre-treatment culture performed
  - had a Test of Cure Visit
  - had not received any other presumably effective antimicrobial agent between the pre-treatment and the Test of Cure Visit
  
- **Microbiologically Evaluable Patients** – all clinically evaluable patients with a pre-treatment culture positive for a bacterial pathogen that was susceptible to both study drugs

For additional comments regarding the statistical plan, please refer to Dr. Silliman's review.

Reviewer's Comments

*The estimated clinical response rate for levofloxacin for this indication was appropriate. Therefore, the sample size calculations were reasonable.*

*If they enrolled 30 patients/diagnosis for each treatment arm, that would be equivalent to at least 20% of the evaluable patients. This would be consistent with the Points to Consider document.*

*There was only one patient who received the wrong treatment – randomized to levofloxacin but received gatifloxacin in error. The results of the study are unchanged, however, if this patient is assigned to the levofloxacin arm for analysis.*

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## 8.4.1.1.7 Study Results

## 8.4.1.1.7.1 Description of Patients Enrolled in the Study

## 8.4.1.1.7.1.1 Number of Patients Enrolled

During the time period from 29 August 1997 to 11 May 1998, 410 patients were enrolled. The applicant closed the study to enrollment of patients with abscess/folliculitis on 13 March 1998, due to the large number of patients they had managed to accrue with that diagnosis up to that time. The following table, reproduced from the applicant's study report (Table 8.1, p. 57), indicates the patient enrollment by site, as well the number that were clinically and microbiologically evaluable:

**Patient Enrollment, by Investigator**

Site/Investigator	Number (%) of Patients				
	Enrolled	Treated	Clinically Eligible	Clinically Evaluable	Microbiologically Evaluable
022 B. Miskin	48 (100)	48 (100)	46 (96)	40 (83)	26 (54)
018 T. Jones	32 (100)	31 (97)	31 (97)	31 (97)	26 (81)
028 G. Tarshis	32 (100)	32 (100)	32 (100)	31 (97)	13 (41)
009 M. Dewan	30 (100)	30 (100)	26 (87)	22 (73)	12 (40)
007 J. Champlin	28 (100)	27 (96)	27 (96)	24 (86)	14 (50)
025 J. Rosen	24 (100)	24 (100)	22 (92)	12 (50)	4 (17)
027 M. Sperling	22 (100)	22 (100)	21 (95)	16 (73)	5 (23)
029 K. Wingert	23 (100)	23 (100)	22 (96)	20 (87)	8 (35)
020 M. Faircloth	21 (100)	21 (100)	21 (100)	12 (57)	11 (52)
010 J. Ervin	15 (100)	15 (100)	15 (100)	11 (73)	4 (27)
021 P. McElvaine	15 (100)	15 (100)	14 (93)	10 (67)	4 (27)
023 G. Post	14 (100)	14 (100)	12 (86)	9 (64)	5 (21)
015 S. Green	13 (100)	13 (100)	13 (100)	12 (92)	6 (46)
031 J. Richards	13 (100)	13 (100)	13 (100)	11 (85)	8 (62)
024 R. Rhoades	12 (100)	11 (92)	11 (92)	11 (92)	9 (75)
002 F. Maggiacomo	11 (100)	11 (100)	11 (100)	11 (100)	5 (45)
016 A. Hebert	10 (100)	10 (100)	9 (90)	8 (80)	4 (40)
008 G. Day	9 (100)	9 (100)	9 (100)	9 (100)	4 (44)
026 J. Shavin	9 (100)	9 (100)	9 (100)	8 (89)	2 (22)
001 A. Puopolo	8 (100)	8 (100)	8 (100)	8 (100)	5 (63)
013 R. Glenn	7 (100)	7 (100)	7 (100)	6 (86)	2 (29)

Site/Investigator	Number (%) of Patients				
	Enrolled	Treated	Clinically Eligible	Clinically Evaluable	Microbiologically Evaluable
004 F. Bieberdorf	5 (100)	5 (100)	5 (100)	4 (80)	2 (40)
005 A. Bucko	4 (100)	4 (100)	4 (100)	3 (75)	1 (25)
030 T. Hodges	2 (100)	2 (100)	1 (50)	1 (50)	0
012 L. Gidday	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
014 B. Goffe	1 (100)	1 (100)	1 (100)	1 (100)	0
019 A. Lucky	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
<b>Total</b>	<b>410</b>	<b>407</b>	<b>392</b>	<b>333</b>	<b>180</b>

#### 8.4.1.1.7.1.2 Patient Demographic Data

The following table, adapted from the applicant's Study Report (Table 8.3, p. 62), and Integrated Summary and Safety Report (Table 9.1, p. 362), summarizes the demographic characteristics of the patient population:

#### Demographic Characteristics, All Treated Patients

Characteristic	Gatifloxacin N = 202	Levofloxacin N = 205	Total N = 407
<u>Gender [N (%)]</u>			
Female	108 (53)	111 (54)	219 (54)
Male	94 (47)	94 (46)	188 (46)
<u>Race [N (%)]</u>			
White	162 (80)	165 (80)	327 (80)
Hispanic	26 (13)	23 (11)	49 (12)
Black	10 (5)	11 (5)	21 (5)
Oriental	1 (<1)	3 (1)	4 (<1)
Other	3 (1)	3 (1)	6 (1)
<u>Age (years)</u>			
Mean	39	40	40
Median	38	39	38
Range	18 - 85	18 - 90	18 - 90
< 65	188 (93)	187 (91)	375 (92)
65 - 74	8 (4)	14 (7)	22 (5)
≥ 75	6 (3)	4 (2)	10 (2)

Indication: Uncomplicated Skin/Skin Structure Infections  
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