the medical reviewer is concerned that the inclusion criteria in the protocol could allow inclusion of patients with allergic rhinitis or viral upper respiratory tract infection. The FDA analysis attempted to address this problem as described below.

According to the sponsor, the clinical efficacy rate at the test of cure visit (Day +21 to +37 post-therapy) was 80% for the per protocol population; 95% C.I. = (76%, 84%). For the all-treated patients population, the sponsor's response rate was 81%; 95% C.I. (77%, 85%). Bacteriological efficacy data from this study demonstrates acceptable activity of moxifloxacin against the three major pathogens in acute sinusitis. Specifically, the eradication/presumed eradication rates for the three major pathogens were as follows:

Streptococcus pneumoniae	97% (29/30)
Haemophilus influenzae	80% (24/30)
Moraxella catarrhalis	83% (15/18)

While the eradication/presumed eradication rates for penicillin-resistant (MIC $\geq$2 g/mL) and penicillin-intermediate susceptibility (0.1<MIC<2 g/mL) isolates of *Streptococcus pneumoniae* were 100% (6/6) and 88.9% (8/9), respectively, the small number of isolates obtained in this study would not support labeling for organisms with reduced penicillin susceptibility.

The FDA analysis used the followup visit (Day +27 to +31 post-therapy) as the test of cure visit to ensure sufficient time off therapy to assess treatment response and to be consistent with FDA efficacy analyses of other studies in the NDA. The FDA per protocol population required either purulent nasal discharge and/or malar tenderness/pain to be present at baseline to enhance the likelihood of acute bacterial sinusitis in evaluable patients. Furthermore, the FDA definition of cure required at least improvement of these two "cardinal" symptoms of acute sinusitis at the test of cure visit. The FDA clinical response rate for moxifloxacin at the test of cure visit was 76%; 95% C.I. = (72%, 81%). The lower clinical efficacy rate observed in this study may be attributable to more severe baseline infections in this study population (see *Pretreatment Signs/Symptoms* section above), or the open-label, non-comparative design of this study.

Drug-related adverse events were mainly related to the gastrointestinal (nausea, diarrhea) and nervous systems. Clinically significant laboratory abnormalities as defined by the sponsor were uncommon and in no case required treatment or discontinuation from the study.

The medical officer concludes that the efficacy data from this study support the approval of moxifloxacin for acute sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*. Insufficient data were presented in this study to support labeling for penicillin-resistant and intermediate susceptibility strains of *S. pneumoniae.* The safety profile of moxifloxacin in this study was acceptable.

VI. Study D96-024: "Prospective, Randomized, Double-Blind, Comparison of the Safety and Efficacy of Bay 12-8039 400 mg PO Once Daily for 7 Days versus Cefuroxime Axetil 250 mg BID PO for 10 Days for the Treatment of Patients with Acute Bacterial Maxillary Sinusitis"

A. Overview

1. Objectives:

This trial was designed to compare the safety and clinical efficacy of BAY 12-8039 400 mg administered orally (PO) once a day for 7 days and of cefuroxime axetil 250 mg PO twice a day (BID) for 10 days in the treatment of adults with clinically documented acute bacterial maxillary sinusitis.

MO Comments: See MO Comments under the review for Protocol 100107 for comments regarding cefuroxime-axetil as a comparator agent. The dosage, frequency and duration of cefuroxime therapy are consistent with the approved labeling for this indication.

As noted in Study 0116, the rationale for proposing a 7 day duration of therapy based on pharmacokinetic, pharmacodynamic or other factors was not clearly presented in the protocol. The current medical literature generally recommends at least a ten day course of antimicrobial therapy for this closed space infection[7]. Treatment for shorter periods of time raises concerns regarding undertreatment of infection leading to post-therapy relapse infections.

2. Design

This was a prospective, randomized, double-blind, active-control, parallel-group design comparing BAY 12-8039 (400 mg once daily) and cefuroxime axetil (250 mg BID) for 10 days in the treatment of acute bacterial maxillary sinusitis.

3. Inclusion Criteria:

Refer to review of Study 0161 above--protocol inclusion criteria and medical officer comments are identical.

4. Exclusion Criteria:

- History of allergy to quinolone derivatives and/or cephalosporins. Patients with a history of severe Type I reactions (i.e. severe hypersensitivity, anaphylaxis) to any β-lactam drugs should also be excluded
- Inability to take oral medication
- Treatment with systemic antimicrobial 24 hours or less before enrollment
- Past sinus surgery (not including antral sinus puncture)
- Need for concomitant systemic antimicrobial therapy with agents not specified in this protocol

- History of chronic sinusitis (defined as continuous symptoms for more than 4 weeks or more than 2 episodes of clinically documented sinusitis within the previous 6 months)
- Significant liver impairment, defined as baseline serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) and/or total bilirubin levels more than 3 times the upper limit of normal
- Significant renal insufficiency, i.e., serum creatinine >3.0 mg/dL (>265 µmol/L) or creatinine clearance <30 mL/min/1.73 m^2)
- History of severe cardiac failure (class IV of the New York Heart Association classification)
- History of tendinopathy associated with fluoroquinolones
- Pregnancy, pregnancy that could not be excluded, nursing, or use of unreliable contraception
- Known or suspected bacteremia or meningitis
- Neutrophil count < 1000/mm^3, CD_4 < 200/mm^3 or other conditions associated with significant depression in host defense, including the use of systemic corticosteroids.
- Rapidly fatal underlying disease (death expected within 6 months)
- Participation in a previous trial of BAY 12-8039
- Use of an investigational drug in the last 30 days

MO Comment: Refer to comments for inclusion/exclusion criteria for Study 0116,

5. Randomization/Blinding:

Patients were randomized in a 1:1 ratio to moxifloxacin or cefuroxime axetil. A single continuous stream randomization code was computer generated by Bayer Corporation in blocks of 4. Each center was supplied with sequentially numbered blister packs containing capsules for 10 days All study drugs were encapsulated in opaque gelatin capsules for blinding purposes. As BAY 12-8039 required only once-daily dosing while cefuroxime axetil required BID dosing, patients randomized to treatment with BAY 12-8039 took 1 capsule BID, one containing a 400 mg tablet of BAY 12-8039 and the other containing placebo on dosing days 1 to 7. On the last 3 days of dosing (days 8 to 10), the patients took 1 placebo capsule BID. Patients in the cefuroxime axetil group took a 250 mg tablet of cefuroxime axetil for 10 days in a capsule identical in appearance to the BAY 12-8039 and placebo capsules.

MO Comment: The study was adequately blinded.

6. Study Procedures/Assessments:

Table III: Study Procedures

	Screening Visit[8]	During-Therapy Visit[1]	End-of-Therapy Visit[1]	Follow-up Visit[1]
Informed consent	✓			
Evaluate patient eligibility	✓			
Medical history	✓			
Physical examination	✓			
Sinus x-ray	✓	✓9	✓	✓10
Gram stain and leukocyte count of aspirate	✓	✓2	✓2	✓11
Clinical laboratory tests:				
Hematology, chemistry, urinalysis	✓	✓	✓12	
Theophylline Level[13]	✓	✓	✓	
Pregnancy test[14]	✓		✓	
Clinical evaluation (symptoms and response to treatment)		✓	✓	✓
Bacteriological response			✓	✓
Assess compliance		✓	✓	
Record adverse events		✓	✓	✓15

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8 Screening visit: no more than 48 hours before start of dosing; during-therapy visit: Day 3 to 5 of therapy; end-of-therapy visit: 2 to 4 days after the last dose of study drug; follow-up visit: 27 to 31 days after the last dose of study drug

9 For patients considered therapeutic failures

10 Only if previous x-ray continued to show abnormalities

11 Antral cultures recommended for clinical relapses

12 In case of abnormal laboratory findings judged potentially related to the study drug, laboratory tests were to be repeated at appropriate intervals until the end of the study or until laboratory values returned to normal

13 Only in patients receiving theophylline concomitantly

14 Although a negative urine pregnancy test was sufficient for enrollment, a serum pregnancy test was required before treatment and end of therapy

15 Adverse events were recorded from the first day of treatment to 7 days after the last dose of study drug. Serious adverse events were recorded through the follow-up period (27 to 31 days after the last dose)

7. Evaluability Criteria:

Clinical Efficacy

Patients had to meet all of the following criteria to be considered evaluable for safety:

- Acute sinusitis confirmed at pre-treatment visit by the presence of signs and symptoms of infection
- Sinus x-ray consistent with acute bacterial maxillary sinusitis
- Availability of pre- and post-therapy sinus x-rays
- A patient deemed a clinical failure had to have had at least 48 hours of treatment with study drug (regardless of investigator's evaluation)
- A patient could not be deemed a clinical success who did not have at least 5 days of treatment with study drug (regardless of investigator's evaluation)
- No concomitant systemic antimicrobial agent (up to follow-up visit 27-31 days post-therapy), except in cases of clinical failure
- At least 80% compliance with study drug regimen
- No protocol violation affecting treatment efficacy
- No missing or indeterminate essential data (i.e., affecting the primary efficacy variable

Safety

All patients who took at least one dose of study drug were included in the safety evaluations. Safety was assessed on the basis of adverse events, premature discontinuation of treatment, concomitant medication use, and laboratory test results.

MO Comment: The efficacy and safety evaluability criteria are acceptable.

8. Statistical Methods

Sample size determination

Based on the assumption of true failure rates of 15% for both treatment groups, the maximum allowable difference between treatments (delta) was 15%. Using these assumptions and alpha=0.025 (one-sided), 180 valid patients per group would result in 92% power to test the null hypothesis of inequivalence. With an assumed validity rate of 80%, approximately 225 patients per arm (450 total) would be required.

Efficacy

The primary efficacy endpoint for the study was the overall clinical response at the completion of the followup evaluation as shown in the table below. The final time

windows used for the end of therapy and followup visits were Day 0 to Day +6 post-therapy and Day +21 to +37 post-therapy, respectively. These revised time windows were decided upon prior to unblinding of the study.

Table IV: Definition of Overall Clinical Response

End of Therapy Evaluation	Follow-up Evaluation	Overall Clinical Response
Resolution or indeterminate	Continued resolution	Resolution
Failure	———	Failure
Resolution or indeterminate	Relapse	Failure
Resolution or indeterminate	Indeterminate	Indeterminate

B. Study Results

1. Database Validation

A 10% random sample of all patients enrolled in this trial was generated by the FDA statistical reviewer. The medical officer conducted an audit of all remote data entry (RDE)forms in this sample to assess the accuracy of transcription of data from the case report forms to the data sets used by the sponsor for the efficacy and safety analyses. No errors of transcription were identified by the audit.

MO Comment: The safety and efficacy data were faithfully transcribed from the case report forms to the sponsor's computerized database. The medical officer accepts the data sets submitted by the sponsor with the NDA as an accurate reflection of the study results.

2. Patient Population

A total of 471 patients were originally enrolled in the trial at 36 study sites across the United States and Canada. Data from Study Site 30 was excluded from all analyses after the FDA advised Bayer in July, 1998, that site's investigator had his clinical activities restricted (due to administrative proceedings against him). The remaining 35 centers enrolled a total of 462 patients: 233 patients in the moxifloxacin arm and 229 patients in the cefuroxime arm. According to the sponsor's analysis, 191 (82%) moxifloxacin-treated patients and 193 (84%) cefuroxime-treated patients were evaluable for the per protocol analysis. See Appendix V for a listing of enrollment by study center and treatment arm.

MO Comment: As shown in Appendix V, the percentage of enrolled subjects who were considered evaluable for the per protocol analysis was fairly consistent across treatment centers, and there was a generally uniform distribution of patient enrollments among the centers.

3. Demographics

The following table was compiled by the medical officer from NDA Tables 14.1.2/1.1, 14.1.2/2.1, and 14.1.2/2.2:

DEMOGRAPHIC DATA

POPULATION: ALL PATIENTS VALID FOR EFFICACY

			BAY 12-8039 400MG (N=195)	CEFUROXIME AXETIL (N=196)	TOTAL (N=391)
SEX (P=0.429)	MALE	N (%)	67 (34)	60 (31)	127 (32)
	FEMALE	N (%)	128 (66)	136 (69)	264 (68)
RACE (P=0.680)	CAUCASIAN	N (%)	175 (90)	175 (89)	350 (90)
	BLACK	N (%)	12 (6)	11 (6)	23 (6)
	ASIAN	N (%)	2 (1)	2 (1)	4 (1)
	AMERICAN INDIAN	N (%)		1 (<1)	1 (<1)
	HISPANIC	N (%)	6 (3)	5 (3)	11 (3)
	OTHER	N (%)		2 (1)	2 (<1)
LACTATING (P= .)	MISSING	N (%)	67 (34)	60 (31)	127 (32)
	NO	N (%)	128 (66)	136 (69)	264 (68)
ADEQUATE BIRTH CONTROL (P= .)	MISSING	N (%)	67 (34)	60 (31)	127 (32)
	YES	N (%)	128 (66)	136 (69)	264 (68)
AGE AT ENROLLMENT (YRS) (P=0.912)		N	195	196	391
		MEAN	42.5	42.3	42.4
		STD	13.8	14.8	14.3
		MIN	18.0	19.0	18.0
		MEDIAN	41.0	40.0	40.0
		MAX	82.0	79.0	82.0
WEIGHT (KG) (P=0.093)		N	195	195	390
		MEAN	78.8	75.6	77.2
		STD	19.4	18.1	18.8
		MIN	45.5	44.1	44.1
		MEDIAN	77.3	74.5	76.4
		MAX	130.5	138.2	138.2

MO Comment: Patient randomization for the study resulted in very comparable demographic characteristics for the two treatment arms for the per protocol population.

4. Reasons for Nonevaluability

As shown in the following table from the NDA (Volume 231, page 60), 42 patients in the moxifloxacin arm and 36 patients in the cefuroxime arm were excluded from the per protocol population. The most common reasons were use of prohibited medications and violations of the time schedule, inclusion/ exclusion criteria or missing primary efficacy determination.

Reason for Exclusion from Efficacy Analysis

Reason for Exclusion	BAY 12-8039 (N=233)[1]	Cefuroxime Axetil (N=229)[1]
Violation of inclusion/exclusion criteria	9 (4%)	5 (2%)
Random code broken	2 (<1%)	0 (0%)
Not treated	1 (<1%)	0 (0%)
Noncompliance with treatment regimen	0 (0%)	1 (<1%)
Duration of treatment insufficient	3 (1%)	3 (1%)
Violation of time schedule	9 (4%)	9 (4%)
Consent withdrawn	1 (<1%)	0 (0%)
Essential data missing or invalid	12 (5%)	9 (4%)
Lost to follow-up	1 (<1%)	0 (0%)
Use of prohibited concomitant medication	4 (2%)	9 (4%)
Total excluded from efficacy analysis	42 (18%)	36 (16%)

MO Comment: The reasons for exclusion from the per protocol population are consistent with the per protocol evaluability criteria. Aside from a slightly higher rate of prohibited concomitant medications in cefuroxime patients and inclusion/exclusion criteria violations in moxifloxacin patients, the two arms appear to be balanced with respect to reasons for exclusion.

As in the review of Study 100107, the reviewer is concerned that the inclusion criteria as outlined in the protocol may have allowed inclusion of patients with conditions other than acute bacterial sinusitis. In order to lessen the likelihood of including patients with viral or allergic disease, the FDA per protocol population required at least one of the two "cardinal" signs/symptoms (purulent nasal discharge, malar pain/tenderness) rated by the investigators which are more indicative of acute bacterial sinusitis than viral or allergic disease.

5. Description of Current Infection/Prognostic Factors

The following table was obtained from the NDA (Volume 231, page 98):

DESCRIPTION OF ACUTE SINUSITIS

POPULATION: ALL PATIENTS VALID FOR EFFICACY

			BAY 12-8039 400MG (N=195)	CEFUROXIME AXETIL (N=196)	TOTAL (N=391)
LOCATION OF INFECTION (P=0.402)	MAXILLARY LEFT	N (%)	40 (21)	51 (26)	91 (23)
	MAXILLARY RIGHT	N (%)	49 (25)	49 (25)	98 (25)
	MAXILLARY BILATE	N (%)	106 (54)	96 (49)	202 (52)
SEVERITY OF INFECTION (P=0.688)	MILD	N (%)	12 (6)	11 (6)	23 (6)
	MODERATE	N (%)	147 (75)	142 (72)	289 (74)
	SEVERE	N (%)	36 (18)	43 (22)	79 (20)
BILATERAL EPISODES LAST 6 MOS (P=0.057)	MISSING	N (%)	4 (2)	2 (1)	6 (2)
	0	N (%)	169 (87)	165 (84)	334 (85)
	1	N (%)	13 (7)	25 (13)	38 (10)
	2	N (%)	9 (5)	4 (2)	13 (3)
EPISODES (RIGHT) LAST 6 MOS (P=0.610)	MISSING	N (%)	4 (2)	2 (1)	6 (2)
	0	N (%)	186 (95)	188 (96)	374 (96)
	1	N (%)	5 (3)	5 (3)	10 (3)
	2	N (%)		1 (<1)	1 (<1)
EPISODES (LEFT) LAST 6 MOS (P=0.191)	MISSING	N (%)	4 (2)	2 (1)	6 (2)
	0	N (%)	184 (94)	191 (97)	375 (96)
	1	N (%)	7 (4)	3 (2)	10 (3)

P-VALUES FOR CATEGORICAL VARS OBTAINED USING A CHI-SQUARED TEST.

MO Comment: The groups were very comparable with respect to location and severity of the present infection. It is unlikely that many patients with underlying chronic sinusitis or recurrent acute sinusitis were enrolled since most patients reported no sinus infections in the last 6 months.

6. Pretreatment Signs/Symptoms

The following table was obtained from the NDA (Volume 231, page 63):

Severity of Pretherapy Signs and Symptoms

	BAY 12-8039			Cefuroxime Axetil		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Frontal headache	19%	42%	26%	16%	40%	31%
Malar tenderness/pain	16%	43%	20%	18%	41%	20%
Nasal congestion	12%	49%	37%	11%	42%	43%
Post-nasal drainage/discharge	13%	49%	35%	14%	53%	32%
Cough/throat clearing	25%	46%	21%	23%	40%	30%
Purulent nasal drainage	16%	52%	24%	11%	45%	33%

Excerpted from Table 14.1/8

MO Comment: The treatment groups were adequately balanced with respect to baseline symptoms by severity, although the cefuroxime arm tended to have a higher percentage of patients reporting severe symptoms.

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7. Reasons for Discontinuations

The following table was obtained from the NDA (Volume 231, page 59):

Table V: Summary of Patient Disposition

	BAY 12-8039	Cefuroxime Axetil
Randomized	238	233
Completed study	223 (94%)	226 (97%)
Premature withdrawals/discontinuations	15 (6%)	7 (3%)
Reason for withdrawal/discontinuation (p = 0.088)[1]		
Adverse event (p = 0.134)[1]	11 (5%)	5 (2%)
Consent withdrawn	1 (<1%)	0 (0%)
Lost to follow-up	2 (<1%)	0 (0%)
Protocol violation	1 (<1%)	2 (<1%)

MO Comment: As shown above, adverse events were the most common reason for discontinuation and were more common in the moxifloxacin arm.

8. Radiographic Findings

The following table summarize the medical officer's analysis of the radiographic data set submitted in the NDA:

Pre-treatment Radiographic Data for Maxillary Sinuses
Protocol D96-024
Safety and Efficacy Populations

Finding	Number (%) of Patients					
	Moxifloxacin		Cefuroxime		Total	
	ITT N=233	Eval N=191	ITT N=229	Eval N=193	ITT N=462	Eval N=384
Mucosal Thickening ≥ 6 mm	159(68)	130(68)	155(68)	131(68)	314(68)	261(68)
Opacification	114(49)	90(47)	110(48)	91(47)	224(48)	181(47)
Air/Fluid Level	88(38)	71(37)	88(38)	74(38)	176(38)	145(38)

MO Comment: The treatment arms were similar in radiological findings consistent with acute sinusitis.

9. Study Drug Exposure

Refer to NDA Table 14.1.18 for complete details of study drug usage. Compliance with both treatment regimens was excellent: 99.6% of moxifloxacin-treated patients and 100% of cefuroxime-treated patients in the safety population received between 17 and 20 doses of study medication.

10. Efficacy

Clinical Efficacy

The following table summarizes the sponsor's evaluation of clinical response in patients valid for efficacy:

Clinical Efficacy of Moxifloxacin and Cefuroxime in Acute Sinusitis
Overall Clinical Response (per Sponsor)
Study D96-024

Drug	Per Protocol Patients		All-Treated Patients	
	Efficacy Rate	95% C.I.	Efficacy Rate	95% C.I.
Moxifloxacin	81% (154/191)	(-17.1, -3.8)	81% (164/203)	(-17.2, -4.3)
Cefuroxime	91% (176/193)		92% (187/204)	

MO Comments: The overall clinical response rate at the sponsor's test of cure visit (Day +21 to +37 post-therapy) was notably higher in the cefuroxime arm. The 95% confidence interval for the difference in efficacy rates failed to meet the protocol-specified criteria for demonstrating clinical equivalence of moxifloxacin to cefuroxime in both the per protocol and all-treated patients populations. The success rates were generally consistent across treatment centers although two treatment centers showed particularly large differences in efficacy rates for evaluable patients. Center 37 had a success rate of 86% (6/7) for cefuroxime and 22% (2/9) for moxifloxacin, and Center 12 had a success rate of 100% (3/3) for cefuroxime and 33% (1/3) for moxifloxacin.

As previously described, the FDA evaluable population had to have at least one of the cardinal symptoms of acute sinusitis at baseline (i.e., malar pain/tenderness or purulent nasal discharge). Consistent with the sponsor's definition of cure, these symptoms had to be resolved or improved at the test of cure visit to consider the patient a clinical cure. To ensure adequate time off therapy to assess treatment response, the FDA analysis used the followup visit (Day +27 to +31 post-therapy) as the test of cure visit. Interestingly, the FDA analysis (table below) showed that the efficacy rate for the moxifloxacin arm was decreased while the rate for the cefuroxime arm increased compared to the sponsor's analysis. These results led to an even less favorable confidence interval for the difference in efficacy rate between treatment arms.

Clinical Efficacy (per MO) of Gatifloxacin and Moxifloxacin in Acute Sinusitis in Per Protocol Patients at Test of Cure Visit
Study D96-024

Drug	Per Protocol Patients	
	Efficacy Rate	95% C.I.
Moxifloxacin	75.1% (139/185)	(-21.8%, -5.3%)
Cefuroxime	88.7% (165/186)	

In summary, both the sponsor and FDA analysis of the clinical efficacy data for this study fail to demonstrate equivalence of moxifloxacin 400 mg po for 7 days to cefuroxime 250 mg po bid for 10 days in the treatment of patients with acute sinusitis. Studies 0161, 0116, and 100107 (reviewed above) showed that a 10-day moxifloxacin treatment regimen meets criteria for clinical equivalence to a 10-day course of cefuroxime. Thus, a likely reason for the difference in efficacy rates observed in this study is insufficient

duration of moxifloxacin therapy. Accordingly, the medical literature currently recommends a minimum of 10 days of antimicrobial therapy for this closed space infection[7].

11. Safety

Deaths

No deaths were reported in this study.

Serious Adverse Events

Two serious adverse events occurred in the moxifloxacin arm and one occurred in the cefuroxime arm. Patient 9-427 was a diabetic patient who developed somnolence and worsening of pretreatment hyperglycemia (from 291 to 601 mg/dL) during the first several days of moxifloxacin therapy. He discontinued therapy, and both events were judged to be possibly related to study drug therapy. Patient 28-113 had a history of coronary artery disease and hypertension. He developed blindness in the upper quadrant of his left eye 27 days after completing study drug therapy due to ischemia of the optic nerve. This event was not felt to be related to moxifloxacin therapy.

All Adverse Events

Adverse events occurred slightly more frequently in the moxifloxacin arm (51% of treated patients) compared to the cefuroxime arm (44% of treated patients).
The following table from the NDA (Volume 231, page 72) shows adverse events with an incidence of at least 2% in either treatment arm without respect to causality:

Adverse Events Occurring in at Least 2% of Patients in Either Treatment Group

Adverse Event	BAY 12-8039 (n=232)	Cefuroxime Axetil (n=229)
Any event	119 (51%)	101 (44%)
Headache	11 (5%)	13 (6%)
Abdominal pain	9 (4%)	0 (0%)
Back pain	2 (<1%)	4 (2%)
Accidental injury	1 (<1%)	4 (2%)
Syncope	4 (2%)	2 (<1%)
Nausea	35 (15%)	14 (6%)
Diarrhea	26 (11%)	15 (7%)
Dyspepsia	8 (3%)	7 (3%)
Dry mouth	5 (2%)	2 (<1%)
Vomiting	6 (3%)	0 (0%)
Flatulence	4 (2%)	3 (1%)
Myalgia	0 (0%)	4 (2%)
Dizziness	12 (5%)	7 (3%)
Insomnia	6 (3%)	4 (2%)
Anxiety	5 (2%)	0 (0%)
Somnolence	2 (<1%)	4 (2%)
Pharyngitis	4 (2%)	2 (<1%)
Taste perversion	5 (2%)	7 (3%)
Vaginal moniliasis	3 (1%)	6 (3%)

MO Comment: The majority of adverse events in both groups were related to the digestive system with nausea, diarrhea and abdominal pain more common in the moxifloxacin arm.

The following table from the study report (Volume 231, page 73) shows drug-related adverse events of at least 2% incidence for either treatment arm:

Drug-Related Adverse Events Occurring in at Least 2% of Either Treatment Group

Adverse Event	BAY 12-8039 (n=232)	Cefuroxime Axetil (n=229)
Any event	88 (38%)	72 (31%)
Headache	4 (2%)	7 (3%)
Abdominal pain	9 (4%)	0 (0%)
Nausea	33 (14%)	12 (5%)
Diarrhea	26 (11%)	15 (7%)
Dyspepsia	7 (3%)	5 (2%)
Dry mouth	5 (2%)	0 (0%)
Vomiting	5 (2%)	0 (0%)
Flatulence	4 (2%)	2 (<1%)
Dizziness	10 (4%)	4 (2%)
Insomnia	5 (2%)	2 (<1%)
Anxiety	4 (2%)	0 (0%)
Somnolence	2 (<1%)	4 (2%)
Taste perversion	5 (2%)	7 (3%)
Vaginal moniliasis	3 (1%)	5 (2%)

MO Comment: The overall rate of drug-related adverse events was slightly higher for the moxifloxacin arm compared to the cefuroxime arm and events were predominantly related to the gastrointestinal and nervous systems. Twelve moxifloxacin patients and 5 cefuroxime patients discontinued due to adverse events. Six of the twelve moxifloxacin patients discontinued to the gastrointestinal (nausea, vomiting, diarrhea, abdominal pain) events. Of note, one moxifloxacin patient developed a probable Type I hypersensitivity reaction (facial swelling, neck welt/pruritis, shortness of breath) on the second day of therapy which resolved without treatment following cessation of therapy.

The following table from the study report (Table 14.3.5/5)shows clinically significant lab changes (as defined by the sponsor in the table):

CLINICALLY SIGNIFICANT CHANGES IN LABORATORY VALUES
POPULATION: PATIENTS VALID FOR ANALYSIS OF SAFETY

LABORATORY TEST	CLINICALLY SIGNIFICANT CHANGE FROM BASELINE	BAY 12-8039 400MG N	TOTAL@	(%)	CEFUROXIME AXETIL N	TOTAL@	(%)
HEMATOLOGY							
HEMATOCRIT (%)	DECREASE OF 20 % FROM BASELINE	0	235	(0)	0	231	(0)
HEMOGLOBIN (G/DL)	DECREASE OF 2 FROM BASELINE	2	235	(1)	6	231	(3)
PLATELETS (PER CUMM)	DECREASE OF 25 % FROM BASELINE	16	235	(7)	17	231	(7)
BLOOD CHEMISTRY							
SGOT/AST (U/L)	INCREASE OF 100 % OVER BASELINE	9	236	(4)	5	232	(2)
SGPT/ALT (U/L)	INCREASE OF 100 % OVER BASELINE	12	236	(5)	12	231	(5)
SGOT/AST (U/L)	INCREASE OF 10 FROM BASELINE	16	236	(7)	14	232	(6)
SGPT/ALT (U/L)	INCREASE OF 10 FROM BASELINE	23	236	(10)	25	231	(11)
BILIRUBIN, TOTAL (MG/DL	INCREASE OF 200 % OVER BASELINE	1	236	(0)	0	232	(0)
CREATININE (MG/DL)	INCREASE OF 50 % OVER BASELINE	5	236	(2)	3	231	(1)
	INCREASE OF 0.6 FROM BASELINE	1	236	(0)	1	231	(0)
BUN (MG/DL)	INCREASE OF 75 % OVER BASELINE	14	236	(6)	13	232	(6)
ALKALINE PHOSPHATASE (U	INCREASE OF 100 % OVER BASELINE	0	236	(0)	1	231	(0)
	INCREASE OF 50 FROM BASELINE	1	236	(0)	1	231	(0)

@ NUMBER OF PATIENTS WITH PRE-TREATMENT AND POST-TREATMENT LABORATORY TEST.

MO Comment: Overall, moxifloxacin and cefuroxime had very similar profiles with respect to the incidence of laboratory abnormalities. One patient in each treatment arm discontinued due to liver function test abnormalities. The moxifloxacin patient was a 23 year old male who, in addition to sinus complaints, had abdominal pain, diarrhea with bloody stools prior to enrollment. His GGT level rose from 218 U/L at enrollment to 396 U/L on Day 4 of the study. Other Day 4 labs were as follows: AST 65 U/L, ALT 131 U/L, alkaline phosphatase 257 U/L. The patient discontinued study drug and six days later his liver function tests had returned to normal. The event was judged as possibly related to study drug therapy.

C. Medical Officer Summary/Conclusions

This prospective, randomized study compared the safety and efficacy of moxifloxacin 400 mg po qd for 7 days to cefuroxime 250 mg po bid for 10 days in patients with acute sinusitis at various study sites throughout the United States and Canada. As noted in the review for Protocol 100107, the medical reviewer is concerned that the inclusion criteria in the protocol could allow enrollment of patients with allergic rhinitis or viral upper respiratory tract infection. The FDA analysis attempted to address this problem as described below.

According to the sponsor, the clinical efficacy rates at the test of cure visit (Day +21 to +37 post-therapy) were 81%% and 91% for the per protocol moxifloxacin and cefuroxime treatment arms, respectively; 95% C.I. =(-17.1%, -3.8%). For the all-treated patients population, the sponsor's response rates were 81% for the moxifloxacin arm and 92% for the cefuroxime arm; 95% C.I (-17.2%, -4.3%). These results fail to meet the protocol-defined criteria for clinical equivalence (delta = 0.15) of moxifloxacin to cefuroxime.

The FDA analysis used the followup visit (Day +27 to +31 post-therapy) as the test of cure visit to allow sufficient time off therapy to assess treatment response. The FDA per protocol population required either purulent nasal discharge and/or malar tenderness/pain to be present at baseline to enhance the likelihood of acute bacterial sinusitis in evaluable patients. Furthermore, the FDA definition of cure required at least improvement of these two "cardinal" symptoms of acute sinusitis at the test of cure visit. Response rates for moxifloxacin and cefuroxime at the test of cure visit were 75.1% and 88.7%, respectively; 95% C.I. = (-21.8%, -5.3%). Again, protocol-defined criteria for equivalence are clearly not met. However, Studies 0161, 0116, and 100107 (reviewed above) showed that a 10-day moxifloxacin treatment meets criteria for clinical equivalence to a 10-day course of cefuroxime. Thus, a likely reason for the difference in efficacy rates observed in this study is insufficient duration of moxifloxacin therapy. Accordingly, the medical literature currently recommends a minimum of 10 days of antimicrobial therapy for this closed space infection[7].

Drug-related adverse events occurred slightly more commonly in the moxifloxacin group (38%) compared to the control group (31%), and were mainly related to the gastrointestinal (nausea, diarrhea, abdominal pain) and nervous (anxiety, insomnia, dizziness) systems. The incidence of laboratory abnormalities was similar between the two treatment arms.

The medical officer concludes that the efficacy data from this study do not support the approval of a seven-day treatment regimen of moxifloxacin for the acute sinusitis indication. The safety profile of moxifloxacin in this study was acceptable.

VII. References:

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VIII. APPENDIX I

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
1	BRUYA	10MAR98	26JUL98	BAY 12-8039 400MG QD	7	7	7	7	7
				CEFUROXIME AXETIL	8	8	8	4	4
				TOTAL	15	15	15	11	11
2	HARPER	16MAY98	05JUN98	BAY 12-8039 400MG QD	0	0	0	0	0
				CEFUROXIME AXETIL	2	2	2	1	2
				TOTAL	2	2	2	1	2
3	KNIGHT	04MAR98	25JUL98	BAY 12-8039 400MG QD	9	9	9	9	9
				CEFUROXIME AXETIL	9	9	9	9	9
				TOTAL	18	18	18	18	18
4	LAFORCE	09MAR98	15MAY98	BAY 12-8039 400MG QD	2	2	2	2	2
				CEFUROXIME AXETIL	3	3	3	2	3
				TOTAL	5	5	5	4	5
5	NOLEN	12MAR98	02APR98	BAY 12-8039 400MG QD	1	1	1	1	1
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	2	2	2	2	2
6	SOKOL	06MAR98	26JUL98	BAY 12-8039 400MG QD	9	9	9	9	9
				CEFUROXIME AXETIL	9	9	9	8	9
				TOTAL	18	18	18	17	18
7	SPERLING	18MAR98	23JUN98	BAY 12-8039 400MG QD	4	4	4	4	3
				CEFUROXIME AXETIL	4	4	4	4	4
				TOTAL	8	8	8	8	7
8	BAZ	12MAR98	08JUL98	BAY 12-8039 400MG QD	23	22	22	16	19
				CEFUROXIME AXETIL	23	23	23	18	20
				TOTAL	46	45	45	34	39
9	BLACK	08APR98	31MAY98	BAY 12-8039 400MG QD	2	2	2	2	2
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	6	6	6	5	6
10	CICHON	17MAR98	13JUN98	BAY 12-8039 400MG QD	4	4	4	3	3
				CEFUROXIME AXETIL	3	3	3	2	3
				TOTAL	7	7	7	5	6

BAY 12-8039/ 100107
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

29SEP98

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
11	KASSMAN	22APR98	03MAY98	BAY 12-8039 400MG QD	1	1	1	1	1
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	2	2	2	2	2
12	LITTLEJOHN	19MAR98	15APR98	BAY 12-8039 400MG QD					
1	1	1	0	0					
				CEFUROXIME AXETIL	1	1	1	0	1
				TOTAL	2	2	2	0	1
13	NEWMAN	02APR98	05JUL98	BAY 12-8039 400MG QD	4	4	4	2	4
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	8	8	8	5	8
14	MARKEL	12MAR98	29JUN98	BAY 12-8039 400MG QD	3	3	3	2	3
				CEFUROXIME AXETIL	3	3	3	2	3
				TOTAL	6	6	6	4	6
15	DORFNER	20FEB98	23JUL98	BAY 12-8039 400MG QD	10	10	10	7	8
				CEFUROXIME AXETIL	10	10	10	7	10
				TOTAL	20	20	20	14	18
16	GAROFALO	13APR98	20JUN98	BAY 12-8039 400MG QD	3	3	3	2	2
				CEFUROXIME AXETIL	2	2	2	0	2
				TOTAL	5	5	5	2	4
17	GIVEN	12MAR98	10JUN98	BAY 12-8039 400MG QD	4	4	4	4	4
				CEFUROXIME AXETIL	3	3	3	3	3
				TOTAL	7	7	7	7	7
19	PATRON	26MAR98	21MAY98	BAY 12-8039 400MG QD	2	2	2	2	2
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	3	3	3	3	3
20	STOKER	12MAR98	17JUL98	BAY 12-8039 400MG QD	4	4	4	3	3
				CEFUROXIME AXETIL	4	4	4	4	4
				TOTAL	8	8	8	7	7
21	SUNDWALL	07APR98	26JUN98	BAY 12-8039 400MG QD	10	9	9	6	9
				CEFUROXIME AXETIL	10	9	9	8	8
				TOTAL	20	18	18	14	17

BAY 12-8039/ 100107
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

29SEP98

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
22	ADELGLASS	03APR98	05JUN98	BAY 12-8039 400MG QD	6	5	5	4	5
				CEFUROXIME AXETIL	5	5	5	5	5
				TOTAL	11	10	10	9	10
23	CHAMPLIN	13MAR98	23JUL98	BAY 12-8039 400MG QD	8	8	8	7	7
				CEFUROXIME AXETIL	8	8	8	7	8
				TOTAL	16	16	16	14	15
24	KRAUSE	07APR98	16APR98	BAY 12-8039 400MG QD	0	0	0	0	0
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	1	1	1	1	1
25	BONNET	20MAR98	14MAY98	BAY 12-8039 400MG QD	1	1	1	1	1
				CEFUROXIME AXETIL	2	2	2	2	2
				TOTAL	3	3	3	3	3
26	COSMO	22APR98	01MAY98	BAY 12-8039 400MG QD	1	1	1	1	1
				CEFUROXIME AXETIL	0	0	0	0	0
				TOTAL	1	1	1	1	1
27	IMAM	13MAR98	25JUL98	BAY 12-8039 400MG QD	10	10	10	8	9
				CEFUROXIME AXETIL	11	11	11	11	11
				TOTAL	21	21	21	19	20
28	THOMPSON	17APR98	31MAY98	BAY 12-8039 400MG QD	3	3	3	3	3
				CEFUROXIME AXETIL	4	4	4	3	3
				TOTAL	7	7	7	6	6
29	CASALE	13MAR98	05JUN98	BAY 12-8039 400MG QD	3	3	3	3	3
				CEFUROXIME AXETIL	3	3	3	3	3
				TOTAL	6	6	6	6	6
30	GARNER	04MAY98	11JUN98	BAY 12-8039 400MG QD	2	2	2	2	2
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	3	3	3	3	3
31	JANNETTI	05MAR98	26JUL98	BAY 12-8039 400MG QD	25	24	24	21	22
				CEFUROXIME AXETIL	26	26	26	25	25
				TOTAL	51	50	50	46	47

BAY 12-8039/ 100107
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

29SEP98

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
32	MAGGIACOMO	17MAR98	06JUN98	BAY 12-8039 400MG QD	2	2	2	2	2
				CEFUROXIME AXETIL	2	2	2	2	2
				TOTAL	4	4	4	4	4
34	FLENNIKEN	11MAR98	13JUN98	BAY 12-8039 400MG QD	6	6	6	6	6
				CEFUROXIME AXETIL	7	7	7	6	7
				TOTAL	13	13	13	12	13
35	PUOPOLO	18MAR98	19JUL98	BAY 12-8039 400MG QD	5	5	5	5	4
				CEFUROXIME AXETIL	6	6	6	6	6
				TOTAL	11	11	11	11	10
36	MORIN	15APR98	24APR98	BAY 12-8039 400MG QD	1	1	1	1	1
				CEFUROXIME AXETIL	0	0	0	0	0
				TOTAL	1	1	1	1	1
37	DEABATE	09APR98	12JUN98	BAY 12-8039 400MG QD	7	7	7	6	7
				CEFUROXIME AXETIL	8	8	8	6	7
				TOTAL	15	15	15	12	14
38	PATRICK	05MAR98	23JUL98	BAY 12-8039 400MG QD	4	4	4	4	4
				CEFUROXIME AXETIL	2	2	2	2	2
				TOTAL	6	6	6	6	6
39	KLIMAS	26MAR98	17JUN98	BAY 12-8039 400MG QD	1	1	1	0	0
				CEFUROXIME AXETIL	2	2	2	1	2
				TOTAL	3	3	3	1	2
40	KALINER	05MAR98	01JUN98	BAY 12-8039 400MG QD	3	3	3	2	2
				CEFUROXIME AXETIL	4	4	4	4	3
				TOTAL	7	7	7	6	5
42	ORCHARD	28MAR98	17JUL98	BAY 12-8039 400MG QD	15	15	15	12	12
				CEFUROXIME AXETIL	15	15	15	14	14
				TOTAL	30	30	30	26	26
43	FERRARO	19MAR98	19JUL98	BAY 12-8039 400MG QD	5	5	5	5	5
				CEFUROXIME AXETIL	4	4	4	4	4
				TOTAL	9	9	9	9	9

BAY 12-8039/ 100107
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

29SEP98

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
44	KUDRYK	26MAR98	30APR98	BAY 12-8039 400MG QD	2	2	2	2	2
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	3	3	3	3	3
45	BURKE	21MAR98	23JUL98	BAY 12-8039 400MG QD	26	26	26	23	24
				CEFUROXIME AXETIL	26	26	26	20	24
				TOTAL	52	52	52	43	48
46	LAWRENCE	19MAR98	22JUN98	BAY 12-8039 400MG QD	3	3	3	1	2
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	7	7	7	4	6
47	RESNICK	09MAR98	18JUL98	BAY 12-8039 400MG QD	7	7	7	7	7
				CEFUROXIME AXETIL	6	6	6	6	6
				TOTAL	13	13	13	13	13
48	WALD	14MAR98	12JUL98	BAY 12-8039 400MG QD	8	8	8	5	7
				CEFUROXIME AXETIL	10	10	10	9	9
				TOTAL	18	18	18	14	16
49	RICTOR	12MAR98	24JUL98	BAY 12-8039 400MG QD	10	10	10	10	10
				CEFUROXIME AXETIL	11	11	11	11	11
				TOTAL	21	21	21	21	21
50	GRINGERI	02JUL98	06JUL98	BAY 12-8039 400MG QD	0	0	0	0	0
				CEFUROXIME AXETIL	1	1	1	0	0
				TOTAL	1	1	1	0	0
ALL CENTERS		28FEB98	26JUL98	BAY 12-8039 400MG QD	267	263	263	223	239
				CEFUROXIME AXETIL	275	274	274	234	257
				TOTAL	542	537	537	457	496

APPENDIX II

PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
			PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID
REGION	COUNTRY	CENTER NO.												
REGION: GERMANY	FEDERAL REPUBLIC OF GERMANY	26	2	2	1		1	1	1		3	3	2	
		27	6	6	6	3	6	6	5	2	12	12	11	5
		28	2	2	2	1	2	2	1	1	4	4	3	2
		29	19	19	18	6	19	19	18	6	38	38	36	12
		30	6	6	4	2	6	6	4	3	12	12	8	5
		31	1	1	1	1	1	1	1		2	2	2	1
		32	3	3	3		4	4	3	3	7	7	6	3
		33	8	8	6		8	8	8		16	16	14	
		36	6	6	5	3	7	7	6	1	13	13	11	4
		39	4	4	4	2	3	3	3		7	7	7	2
		40	4	4	3	1	4	4	4	3	8	8	7	4
		115	1	1	1	1	1	1	1	1	2	2	2	2
		124	2	2	2		2	2	2	1	4	4	4	1
		125	4	4	4	2	4	4	4	2	8	8	8	4
		127	2	2	1	1	2	2	1	1	4	4	2	2
		132	1	1	1		2	2	2		3	3	3	
		134	2	2	2		2	2	1		4	4	3	
		ALL	73	73	64	23	74	74	65	24	147	147	129	47
	ALL		73	73	64	23	74	74	65	24	147	147	129	47
REGION: FRANCE	COUNTRY	CENTER NO.												
	FRANCE	74	3	3	3	3	4	4	4	3	7	7	7	6
		75	2	2	2		2	2	2	1	4	4	4	1
		78	1	1	1	1	2	2	2	1	3	3	3	2

(CONTINUED)

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COMPARISON OF EFFICACY AND SAFETY OF BAY 12-8039 VERSUS CEFUROXIME-AXETIL FOR THE TREATMENT OF ACUTE SINUSITIS

TABLE 14.1.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID
REGION: FRANCE	FRANCE	81	4	4	3		4	4	4	1	8	8	7	1
		82	4	4	2	2	4	4	4	3	8	8	6	5
		84	2	2	2	1	2	2	2	2	4	4	4	3
		85	3	3	3	2	4	4	4	1	7	7	7	3
		88	4	4	3	3	4	4	3	1	8	8	6	4
		89	16	16	13	7	16	16	15	5	32	32	28	12
		91	15	15	12	6	14	14	12	4	29	29	24	10
		92	6	6	6	3	6	6	3		12	12	9	3
		126					1	1			1	1		
		128	1								1			
		ALL	61	60	50	28	63	63	55	22	124	123	105	50
	ALL		61	60	50	28	63	63	55	22	124	123	105	50
REGION: NORTHERN EUROPE-GREAT BRITAIN	COUNTRY	CENTER NO.												
	GREAT BRITAIN (UNITED KINGDOM)	133					1	1			1	1		
		136	2	2	1		4	4	3		6	6	4	
		210	4	4	3		4	4	2		8	8	5	
		215	2	2	2		2	2	1		4	4	3	
		216	2	2	2		2	2	2		4	4	4	
		220	1	1			1	1			2	2		
		234	1	1							1	1		
		239	1	1	1						1	1	1	
		ALL	13	13	9		14	14	8		27	27	17	

(CONTINUED)

BAY 12-8039 / STUDY NUMBER 0161 11:03 Wednesday, August 26, 1998

COMPARISON OF EFFICACY AND SAFETY OF BAY 12-8039 VERSUS CEFUROXIME-AXETIL FOR THE TREATMENT OF ACUTE SINUSITIS

TABLE 14.3.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION: FRANCE	FRANCE	81	4	4	3		4	4	4	1	8	8	7	1
		82	4	4	2	2	4	4	4	3	8	8	6	5
		84	2	2	2	1	2	2	2	2	4	4	4	3
		85	3	3	3	2	4	4	4	1	7	7	7	3
		88	4	4	3	3	4	4	3	1	8	8	6	4
		89	16	16	13	7	16	16	15	5	32	32	28	12
		91	15	15	12	6	14	14	12	4	29	29	24	10
		92	6	6	6	3	6	6	3		12	12	9	3
		126					1	1			1	1		
		128	1								1			
		ALL	61	60	50	28	63	63	55	22	124	123	105	50
	ALL		61	60	50	28	63	63	55	22	124	123	105	50
REGION: NORTHERN EUROPE-GREAT BRITAIN	COUNTRY	CENTER NO.												
	GREAT BRITAIN (UNITED KINGDOM)	133					1	1			1	1		
		136	2	2	1		4	4	3		6	6	4	
		210	4	4	3		4	4	2		8	8	5	
		215	2	2	2		2	2	1		4	4	3	
		216	2	2	2		2	2	2		4	4	4	
		220	1	1			1	1			2	2		
		234	1	1							1	1		
		239	1	1	1						1	1	1	
		ALL	13	13	9		14	14	8		27	27	17	

(CONTINUED)

BAY 12-8039 / STUDY NUMBER 0161 11:03 Wednesday, August 26, 1998

COMPARISON OF EFFICACY AND SAFETY OF BAY 12-8039 VERSUS CEFUROXIME-AXETIL FOR THE TREATMENT OF ACUTE SINUSITIS

TABLE 14.1.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION: NORTHERN EUROPE+GREAT BRITAIN	LITHUANIA	13	12	12	12	7	13	13	13	7	25	25	25	14
		130	12	12	12	5	12	12	12	6	24	24	24	11
		131	10	10	10	8	10	10	10	4	20	20	20	12
		ALL	34	34	34	20	35	35	35	17	69	69	69	37
	FINLAND	CENTER NO.												
		72	6	6	6	2	5	5	5	1	11	11	11	3
		73	4	4	4	2	4	4	4	2	8	8	8	4
		ALL	10	10	10	4	9	9	9	3	19	19	19	7
	ALL		57	57	53	24	58	58	52	20	115	115	105	44
REGION: GREECE+ISRAEL	COUNTRY	CENTER NO.												
	GREECE	187	36	36	36	2	36	36	36		72	72	72	2
		ALL	36	36	36	2	36	36	36		72	72	72	2
	ISRAEL	CENTER NO.												
		42	8	8	7	3	8	8	8	3	16	16	15	6
		43	4	4	4	3	5	5	3	2	9	9	7	5
		44	7	7	3	3	7	7	3	1	14	14	6	4
		ALL	19	19	14	9	20	20	14	6	39	39	28	15
	ALL		55	55	50	11	56	56	50	6	111	111	100	17
ALL			246	245	217	86	251	251	222	72	497	496	439	158

APPENDIX III

TABLE 14.1.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039 400 MG				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICROBIOL. VALID
REGION: GERMANY	FEDERAL REPUBLIC OF GERMANY	24	2	2	2	1	1	1	1	1	3	3	3	2
		25	5	5	5	1	5	5	4	3	10	10	9	4
		26	1	1	1	1	1	1	1	1	2	2	2	2
		27	4	4	2	2	5	4	4	1	9	8	6	3
		28	2	2	1	1	2	2			4	4	1	1
		29	9	9	9	5	10	10	10	3	19	19	19	8
		30	8	8	8	4	8	8	8	4	16	16	16	8
		31	4	4	4	3	4	4	4	2	8	8	8	5
		32	2	2	2	1	3	3	2	1	5	5	4	2
		33	6	6	5	5	6	6	5	5	12	12	10	10
		34					1	1	1	1	1	1	1	1
		35	2	2	2	2	3	3	3	1	5	5	5	3
		36	4	4	3	1	5	5	5	5	9	9	8	6
		39	9	8	7	3	10	9	9	2	19	17	16	5
		40	5	5	4	2	5	5	3	2	10	10	7	4
		ALL	63	62	55	32	69	67	60	32	132	129	115	64
	ALL		63	62	55	32	69	67	60	32	132	129	115	64
REGION: SOUTH EUROPE + ISRAEL	COUNTRY	CENTER NO.												
	SPAIN	45	5	5	5	1	6	5	5	1	11	10	10	2
		48	2	2	2	1	3	3	3		5	5	5	1

(CONTINUED)

SAFETY POPULATION EQUALS ITT POPULATION

BAY 12-8039 / STUDY NUMBER 0116 08:11 Tuesday, November 17, 1998

COMPARISON OF EFFICACY AND SAFETY OF BAY 12-8039 AND CEFUROXIME-AXETIL FOR THE TREATMENT OF ACUTE SINUSITIS

TABLE 14.1.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039 400 MG				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
			PATIENTS ENROLLED	VALID FOR ITT*	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT*	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT*	VALID PER PROTOCOL	MICROBIOL. VALID
REGION	COUNTRY	ALL												
REGION: SOUTH EUROPE + ISRAEL	SPAIN		7	7	7	2	9	8	8	1	16	15	15	3
	GREECE	CENTER NO.												
		41	20	20	20	10	20	20	20	8	40	40	40	18
		ALL	20	20	20	10	20	20	20	8	40	40	40	18
	ISRAEL	CENTER NO.												
		42	8	8	6		8	8	8	1	16	16	14	1
		43	5	5	5		4	4	2	2	9	9	7	2
		44	8	8	5	2	9	9	7	3	17	17	12	5
		ALL	21	21	16	2	21	21	17	6	42	42	33	8
	ALL		48	48	43	14	50	49	45	15	98	97	88	29
REGION: FRANCE	COUNTRY	CENTER NO.												
	FRANCE	74	6	6	6	6	6	6	6	6	12	12	12	12
		75	4	4	4	1	4	4	4	1	8	8	8	2
		76					1	1	1	1	1	1	1	1
		77	1	1	1						1	1	1	
		78	4	4	4	3	4	4	4	4	8	8	8	7
		79	1	1	1	1	2	2	2	2	3	3	3	3
		81	4	4	4	2	4	4	4	4	8	8	8	6
		82	4	4	2	1	4	4	4	1	8	8	6	2
		86	4	4	1		4	4			8	8	1	

(CONTINUED)

* SAFETY POPULATION EQUALS ITT POPULATION

08:11 Tuesday, November 17, 1998

BAY 12-8039 / STUDY NUMBER 0116

COMPARISON OF EFFICACY AND SAFETY OF BAY 12-8039 AND CEFUROXIME-AXETIL FOR THE TREATMENT OF ACUTE SINUSITIS

TABLE 14.1.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039 400 MG				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
			PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION	COUNTRY	CENTER NO.												
REGION: FRANCE	FRANCE	85	14	14	10	4	14	14	11	5	28	28	21	9
		87	2	2	2		2	2	2	1	4	4	4	1
		88	4	4	3	1	4	4	4	1	8	8	7	2
		89	14	14	11	3	14	14	13	4	28	28	24	7
		90	2	2	2	1					2	2	2	1
		91	12	11	11	2	12	12	10	7	24	23	21	9
		92	6	6	5	4	6	6	5	1	12	12	10	5
		93	1	1	1		1	1	1		2	2	2	
		ALL	83	82	68	29	82	82	71	38	165	164	139	67
	ALL		83	82	68	29	82	82	71	38	165	164	139	67
REGION: SCANDINAVIA	COUNTRY	CENTER NO.												
	SWEDEN	50	1	1	1	1	1	1	1	1	2	2	2	2
		51	12	12	11	9	12	12	11	6	24	24	22	15
		52	2	2	1	1	2	2	2	2	4	4	3	3
		53	2	2	2		2	2	1	1	4	4	3	1
		54	1	1	1	1					1	1	1	1
		55	4	4	2	1	6	6	5	1	10	10	7	2
		58	6	6	6	4	5	5	5	3	11	11	11	7
		59	4	4	3	2	4	4	4	4	8	8	7	6
		ALL	32	32	27	19	32	32	29	18	64	64	56	37

(CONTINUED)

[1] SAFETY POPULATION EQUALS ITT POPULATION

NDA # 21-061
Acute Sinusitis Indication

08:11 Tuesday, November 17, 1998

BAY 12-8039 / STUDY NUMBER 0116

COMPARISON OF EFFICACY AND SAFETY OF BAY 12-8039 AND CEFUROXIME-AXETIL FOR THE TREATMENT OF ACUTE SINUSITIS

TABLE 14.1.1/1: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP

			TREATMENT GROUP											
			BAY 12-8039 400 MG				CEFUROXIME-AXETIL				ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION: SCANDINAVIA	FINLAND	68	1	1	1						1	1	1	
		72	11	11	11	9	14	14	14	8	25	25	25	17
		73	6	6	6	6	7	7	6	4	13	13	12	10
		All	18	18	18	15	21	21	20	12	39	39	38	27
	ALL		50	50	45	36	53	53	49	30	103	103	96	64
ALL			244	242	211	109	254	251	225	115	498	493	436	224

APPENDIX IV

STUDY PERIODS AND SAMPLE SIZES BY CENTER
(Study D96-023)

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS				
					ENTERED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
1	Adelglass	06DEC96	10FEB97	BAY 12-8039 400MG	4	4	3	0	4
2	Johnson	31OCT96	24MAR97	BAY 12-8039 400MG	38	38	37	6	37
3	Bruya	31OCT96	19JAN97	BAY 12-8039 400MG	12	12	12	1	12
4	Gower	09DEC96	18DEC97	BAY 12-8039 400MG	17	17	13	6	16
5	Morgan	06NOV96	30MAY97	BAY 12-8039 400MG	7	7	6	0	7
6	DeAbate	16JUL97	28OCT97	BAY 12-8039 400MG	8	8	8	0	8
7	Feinman	12NOV96	10FEB97	BAY 12-8039 400MG	25	24	21	9	23
8	Newbill	04DEC96	27OCT97	BAY 12-8039 400MG	21	21	12	3	21
9	Roper	21NOV96	27NOV97	BAY 12-8039 400MG	25	25	22	7	25
10	Collins	31OCT96	13NOV96	BAY 12-8039 400MG	3	3	3	1	3
11	Winther	13FEB97	12MAR97	BAY 12-8039 400MG	6	6	6	1	6
12	Baz	27NOV96	28JAN98	BAY 12-8039 400MG	30	30	29	6	29
13	Bianchi	25OCT96	12JAN97	BAY 12-8039 400MG	24	24	23	2	24
14	Goldberg	30OCT96	24DEC97	BAY 12-8039 400MG	27	27	25	9	26
15	Munk	20NOV96	07MAY97	BAY 12-8039 400MG	8	8	8	1	8
16	Salazar	14NOV96	15APR97	BAY 12-8039 400MG	15	15	12	0	15
17	Sterling	07NOV96	20NOV97	BAY 12-8039 400MG	14	14	13	0	14
18	Walker	10DEC96	16DEC96	BAY 12-8039 400MG	1	1	1	0	1
19	Bywaters	30DEC96	05JAN97	BAY 12-8039 400MG	1	1	1	0	1
20	Geisberg	21NOV96	06FEB97	BAY 12-8039 400MG	7	7	6	0	7
21	Jones	27DEC96	02APR97	BAY 12-8039 400MG	4	4	4	2	4

BAY 12-8039/D96-023
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

29MAY98

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
22	Kobayashi	04DEC96	16FEB97	BAY 12-8039 400MG	16	16	14	2	16
23	Nielson	04NOV96	20JAN98	BAY 12-8039 400MG	33	33	31	13	31
24	Hirsch	22NOV96	16MAR97	BAY 12-8039 400MG	10	10	10	0	10
25	Milgrom	30DEC96	14JAN98	BAY 12-8039 400MG	16	16	16	5	16
ALL CENTERS		25OCT96	28JAN98	BAY 12-8039 400MG	372	371	336	74	364

APPENDIX V

Study D96-024

STUDY PERIODS AND SAMPLE SIZES BY CENTER

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
1	Littlejohn	06DEC96	28FEB97	BAY 12-8039 400MG	6	6	6	4	5
				CEFUROXIME AXETIL	6	6	6	6	6
				TOTAL	12	12	12	10	11
2	Bock	05DEC96	24MAR97	BAY 12-8039 400MG	6	6	6	4	5
				CEFUROXIME AXETIL	6	6	6	5	6
				TOTAL	12	12	12	9	11
3	Champlin	03DEC96	27APR97	BAY 12-8039 400MG	8	8	8	7	7
				CEFUROXIME AXETIL	8	8	8	8	8
				TOTAL	16	16	16	15	15
4	LaForce	03JAN97	30JAN97	BAY 12-8039 400MG	6	6	6	6	6
				CEFUROXIME AXETIL	6	6	6	6	6
				TOTAL	12	12	12	12	12
5	Newman	26NOV96	21APR97	BAY 12-8039 400MG	12	11	11	8	11
				CEFUROXIME AXETIL	12	12	12	11	11
				TOTAL	24	23	23	19	22
6	Schwartz	18DEC96	27MAR97	BAY 12-8039 400MG	6	6	6	4	5
				CEFUROXIME AXETIL	6	6	6	6	6
				TOTAL	12	12	12	10	11
8	Sokol	03DEC96	13MAR97	BAY 12-8039 400MG	8	8	8	6	7
				CEFUROXIME AXETIL	8	8	8	8	8
				TOTAL	16	16	16	14	15
9	Suchyta	20DEC96	21MAR97	BAY 12-8039 400MG	8	8	8	8	7
				CEFUROXIME AXETIL	8	8	8	7	8
				TOTAL	16	16	16	15	15
10	Adelglass	02DEC96	10APR97	BAY 12-8039 400MG	8	8	8	8	8
				CEFUROXIME AXETIL	8	8	8	7	7
				TOTAL	16	16	16	15	15
11	Gompf	09DEC96	26MAR97	BAY 12-8039 400MG	6	6	6	4	6
				CEFUROXIME AXETIL	6	6	6	4	6
				TOTAL	12	12	12	8	12

BAY 12-8039/D96-024
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

10NOV97

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
12	Drehobl	23DEC96	13APR97	BAY 12-8039 400MG	6	6	6	3	5
				CEFUROXIME AXETIL	5	5	5	3	5
				TOTAL	11	11	11	6	10
13	Harper	02DEC96	03MAR97	BAY 12-8039 400MG	10	10	10	9	9
				CEFUROXIME AXETIL	10	10	10	9	10
				TOTAL	20	20	20	18	19
14	Patrick	06JAN97	08MAR97	BAY 12-8039 400MG	6	6	6	6	6
				CEFUROXIME AXETIL	6	6	6	5	6
				TOTAL	12	12	12	11	12
16	Sperling	21NOV96	19JAN97	BAY 12-8039 400MG	8	8	8	8	8
				CEFUROXIME AXETIL	8	8	8	7	7
				TOTAL	16	16	16	15	15
18	Rhoades	20NOV96	04MAR97	BAY 12-8039 400MG	10	10	10	9	10
				CEFUROXIME AXETIL	10	10	10	7	10
				TOTAL	20	20	20	16	20
19	Knight	02JAN97	01MAR97	BAY 12-8039 400MG	10	10	10	9	9
				CEFUROXIME AXETIL	10	10	10	7	10
				TOTAL	20	20	20	16	19
20	Foss	27NOV96	24JAN97	BAY 12-8039 400MG	10	10	10	8	10
				CEFUROXIME AXETIL	10	10	10	10	10
				TOTAL	20	20	20	18	20
21	Krause	30DEC96	06APR97	BAY 12-8039 400MG	2	2	2	2	2
				CEFUROXIME AXETIL	3	3	3	3	3
				TOTAL	5	5	5	5	5
22	Nolen	09DEC96	23MAR97	BAY 12-8039 400MG	8	8	8	6	7
				CEFUROXIME AXETIL	8	8	8	5	6
				TOTAL	16	16	16	11	13
23	Casale	23DEC96	08MAR97	BAY 12-8039 400MG	3	3	3	2	3
				CEFUROXIME AXETIL	3	3	3	3	3
				TOTAL	6	6	6	5	6

BAY 12-8039/D96-024
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TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

10NOV97

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
24	Black	20NOV96	05APR97	BAY 12-8039 400MG	8	8	8	6	8
				CEFUROXIME AXETIL	8	8	8	5	8
				TOTAL	16	16	16	11	16
26	Stafford	17FEB97	13APR97	BAY 12-8039 400MG	6	6	6	4	6
				CEFUROXIME AXETIL	6	6	6	3	6
				TOTAL	12	12	12	7	12
27	Harris	10DEC96	24APR97	BAY 12-8039 400MG	8	8	8	5	7
				CEFUROXIME AXETIL	6	6	6	5	6
				TOTAL	14	14	14	10	13
28	GROSSMAN	18DEC96	07APR97	BAY 12-8039 400MG	6	6	6	6	6
				CEFUROXIME AXETIL	6	6	6	6	6
				TOTAL	12	12	12	12	12
29	Finn	19NOV96	21APR97	BAY 12-8039 400MG	10	10	10	9	9
				CEFUROXIME AXETIL	10	10	10	9	10
				TOTAL	20	20	20	18	19
30	Edwards	20FEB97	04APR97	BAY 12-8039 400MG	5	5	5	4	4
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	9	9	9	7	8
31	Dvorin	12DEC96	24APR97	BAY 12-8039 400MG	4	4	4	3	4
				CEFUROXIME AXETIL	4	4	4	2	4
				TOTAL	8	8	8	5	8
32	Coyle	09DEC96	20FEB97	BAY 12-8039 400MG	10	10	10	8	10
				CEFUROXIME AXETIL	10	10	10	9	10
				TOTAL	20	20	20	17	20
33	Marlow	23JAN97	30MAR97	BAY 12-8039 400MG	4	4	4	4	4
				CEFUROXIME AXETIL	4	4	4	4	4
				TOTAL	8	8	8	8	8
34	Hickman	13JAN97	01MAR97	BAY 12-8039 400MG	4	4	4	2	3
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	8	8	8	5	7

BAY 12-8039/D96-024
SINUSITIS

TABLE 14.1/1
STUDY PERIODS AND SAMPLE SIZES BY CENTER

10NOV97

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
35	Salamoun	07DEC96	26JAN97	BAY 12-8039 400MG	4	4	4	3	3
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	8	8	8	6	7
36	Burge	17JAN97	13MAR97	BAY 12-8039 400MG	3	3	3	3	3
				CEFUROXIME AXETIL	3	3	3	3	3
				TOTAL	6	6	6	6	6
37	Jennings	20NOV96	01JAN97	BAY 12-8039 400MG	10	10	10	9	10
				CEFUROXIME AXETIL	10	10	10	7	9
				TOTAL	20	20	20	16	19
38	Kassman	03JAN97	01MAY97	BAY 12-8039 400MG	4	4	4	4	4
				CEFUROXIME AXETIL	3	3	3	3	3
				TOTAL	7	7	7	7	7
39	Kessler	22NOV96	17APR97	BAY 12-8039 400MG	3	3	3	3	3
				CEFUROXIME AXETIL	4	4	4	4	3
				TOTAL	7	7	7	7	6
40	Reher	19FEB97	01MAR97	BAY 12-8039 400MG	2	2	2	1	2
				CEFUROXIME AXETIL	0	0	0	0	0
				TOTAL	2	2	2	1	2
All	All	19NOV96	01MAY97	BAY 12-8039 400MG	238	237	237	195	222
				CEFUROXIME AXETIL	233	233	233	196	226
				TOTAL	471	470	470	391	448

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX VI

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 (>/= 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)-lactamaseproducing 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. BIAXIN

BIAXIN Filmtab tablets and BIAXIN 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*

NDA # 21-085
Acute Sinusitis Indication

/S/ 9/30/99

Eric Mann M.D., Ph.D.
Medical Officer

Concurrence
HFD590/MTL/HopkinsR /S/ 12/9/99

cc:
NDA 21-085
HFD-590/DivDir/GoldbergerM
HFD-590/MTL/HopkinsR
HFD-590/MO/SacksL
HFD-590/PM/JensenV
HFD-590/Biopharm/MeyerJ
HFD-590/Biostat/ShenL
HFD590/Biostat/SillimanN
HFD590/Pharmtox/EllisA
HFD590/MO/NavarroE
HFD590/MO/MeyerhoffA
HFD590/MO/PowersJoh

V JENSEN

NDA#21085

JUL 16 1999

DIVISION OF CARDIO RENAL DRUG PRODUCTS
CONSULTATION

To: Mark Goldberg, M.D., Division Director,
HFD-590 Division of Special Pathogens and Immunologic Drug Products

From: Maryann Gordon, M.D., Medical Officer, /S/ 7-16-99
HFD-110 Division of Cardio-Renal Drug Products

Through: Shaw Chen, M.D., Ph.D., Supervisor, /S/
HFD 110, Division of Cardio-Renal Drug Products

Raymond Lipicky, M.D., Division Director /S/
HFD 110, Division of Cardio-Renal Drug Products

NDA #21085 (moxifloxacin, BAY 12-8039)
Formulation: oral
Sponsor: Bayer Corporation
Date received: 5/13/99
Request: review the effects of moxifloxacin on QT/QTc intervals.

Introduction: Moxifloxacin is an oral fluoroquinolone under review for the treatment of acute bacterial maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, [redacted] There are numerous other "second generation" quinolones that are approved for use including sparfloxacin and grepafloxacin. Some of these agents are linked to QT prolongation and others are linked to additional toxicities. The Cardio-Renal Division was asked to review the issue of moxifloxacin's effect on the QTc interval.

The following paragraphs briefly describe relevant aspects of the pahrmacokinetic/pharmacodynamic characteristics of moxifloxacin and were taken from the NDA.

- In hepatocyte cultures from rat and human donors, the main biotransformation reactions of moxifloxacin were sulfate and glucuronic acid conjugation to metabolites.
- The recommended dose is 400 mg qd for 5-10 days depending on the indication.
- Overall there was no apparent clinically significant trend in change of vital signs from baseline.
- The absolute bioavailability is approximately 90% and is not affected by food or dairy products.
- Maximum plasma concentration at steady-state with a 400 mg once daily dosage regimen is approximately 4.5 mg/L and is attained 1 to 3 hours after oral dosing.
- Trough concentration averages 0.88 mg/L. The mean steady-state AUC is 34 mg*h/L. Plasma concentrations increase proportionately with dose up to the highest dose tested (800 mg). The elimination half-life from plasma is approximately 12 hours; steady-state is achieved within three days with a 400 mg once daily regimen.
- There are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration. Mean Cmax and AUC were 24% and 29% higher, respectively, in healthy elderly females compared to healthy elderly males.

Background: there is general agreement that moxifloxacin prolongs the QT/QTc interval. Bayer evaluated the relationship between moxifloxacin concentration and QT/QTc[1] lengthening (concentration effect analysis) from data collected in a selection of studies with healthy volunteers conducted in the US,

[1] appendix 7 of NDA #21085

Europe, and Japan with both the oral and intravenous formulations. In addition, there is convincing evidence of an overall increase in QT/QTc interval when the entire data base is examined. These 2 analyses are discussed below.

Part 1.
The concentration effect analysis examined data from

- 17 oral US and European studies (designated US/EU, oral) with doses ranging from 50 to 600 mg,
- 3 intravenous US and European studies (designated US/EU, iv), and
- 3 oral Japanese studies with doses ranging from 100 to 400 mg.

The objective of this analysis was to determine if increasing the concentration of moxifloxacin causes an increase in the QTc interval. Data from a total of 319 patients were included and the ECG data were obtained from automated devices[2]. The QT interval measurements and drug concentrations were obtained closest to Tmax; i.e., 2 to 2.5 hrs for the oral formulation and at the end of the infusion for the iv formulation. The 400 mg dose of moxifloxacin results in a concentration range of 1500-4500 ng/l.

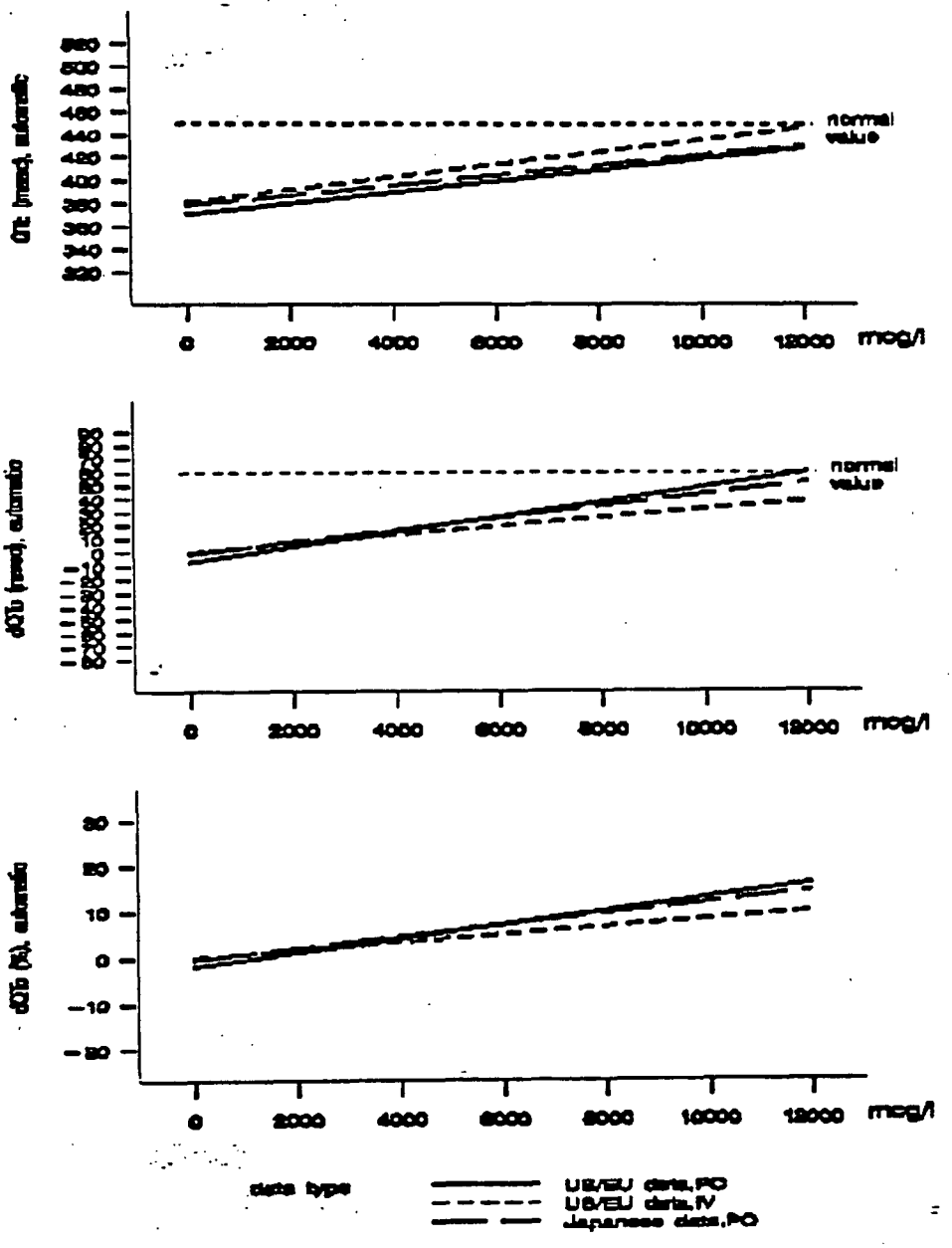
The following comparisons were made:

- Actual QTc interval versus concentration measured at the Tmax,
- delta QTc versus concentration, where delta QTc is the value of QTc at presumed Tmax minus QTc at baseline (0 hours),
- percentage change in QTc (% QTc) versus concentration (measured at the presumed Tmax minus baseline)

Results: The summary of these 3 comparisons are shown below.

[2] although results with manual readings were very similar, the QTc values read automatically were generally lower

Figure 4 : Summary of regression lines (N=319)
Linear regression lines per data type



The slopes of the regression lines are 0.0055 ms/ug/l for the absolute QTc, 0.0057 ms/ug/l for delta QTc, and 0.0015 ms/ug/l for the % QTc change and these are all was statistical significantly different from zero. The corresponding correlation coefficients are 0.25 for the oral US/EU data, 0.39 for the oral Japanese data and 0.54 for the iv US/EU data). The results were independent of formulation (oral versus intravenous) and study location.

In summary, it can be confidently concluded that moxifloxacin prolongs the length of the QTc interval and the prolongation is directly related to drug concentration.

Part 2

When it was realized during development that moxifloxacin prolonged the QT/QTc, adjustments to recruitment were made to safeguard study patients. In May, 1997, the following exclusions were added to ongoing and future protocols:

[redacted]

In addition, protocols began to require that baseline and post-dosing 12-lead ECGs be collected at baseline and at Tmax. A special procedure for the review of ECGs was implemented that required reviewers to read each ECG with no indication of the timing of the ECG or of patient identity or medical history. The QT interval measured was to be the longest one on each tracing, regardless of the lead. As a result, pre- and post-dosing QT intervals were not necessarily from the same lead.

The table below shows the number of patients in the moxifloxacin clinical development program.

	Patients who received oral treatment		
	moxifloxacin	Comparator drug	total
Total patients treated	4926	3415	8341
Patients with valid ecgs^	648+	136	784

^patients in this category had to have paired ECGs that met the ITT-criterion of not having "long followed by short RR interval" syndromes at both baseline and on study, paired ECGs of good technical quality and a post-dosing ECG within the time window of 15 minutes to 6 hours after study drug dosing

+37 patients in this grouping received 200 mg and 611 patients received 400 mg

At total of 8341 patients worldwide (4926 treated with moxifloxacin and 3415 treated with comparative agents) were evaluated for safety of the oral formulation. Of the 8341 patients, only 784 (9% of the total treated population) were considered to have valid ECG evaluations. Therefore, the following information is of limited value because it excludes data from 91% of the treated population.

From this small sample size, the sponsor classified study patients by various changes in QTc. These are shown in the table below.

Percent of patients with valid ECGs#
Number of patients treated

	N=4926^ Moxifloxacin N=596	Clarithromycin N=136	N=3415+ All comparators *except* clarithromycin N=379
QTc: increase ≥30 msec *and* if male ≥450 msec or female ≥470 msec	9	5	5
QTc: any increase and ≥ 500 msec	3	0	1
QTc: increase ≥15%	12	0	4

^patients in this category had to have paired ECGs that met the ITT-criterion of not having "long followed by short RR interval" syndromes at both baseline and on study, paired ECGs of good technical quality and a post-dosing ECG within the time window of 15 minutes to 6 hours after study drug dosing
^includes 200 and 400 mg doses only. The highest dose tested was 800 mg
+includes all comparators

Of the 596 patients (12% of the total number of patients who received moxifloxacin), 9% had an QTc increase by at least 30 msec *and* if male had a QTc ≥450 msec or if female ≥470 msec, 3% had any increase in QTc and a QTc > 500 msec and 12% had at least a 15% increase in QTc from baseline. These percents were higher than what was observed with the comparative drugs.

The table below shows individual moxifloxacin patients from this selected data base who had very large QTc changes from baseline.

Study/center/pt number^	baseline QTc	On drug QTc	Change from baseline QTc
140/278/10544	365 msec	583 msec	218 msec
161/74/28001	367 msec	479 msec	112 msec
140/401/10368	363 msec	472 msec	109 msec
161/81/31002	345 msec	452 msec	107 msec
140/290/10669	439 msec	535 msec	96 msec
~~140/290/10669~~	~~439 msec~~	~~535 msec~~	~~96 msec~~
140/244/10074	334 msec	419 msec	85 msec
161/91/37016	342 msec	424 msec	82 msec
140/271/10255	417 msec	498 msec	81 msec
140/268/10046	452 msec	519 msec	67 msec

^ baseline for patient 140/270/10248 is probably an error so the data was excluded
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There were no patients in the selected clarithromycin group and only 1 patient in the other comparator group who had a QTc increase of more than 80 msec. Again, this is a sampling and not the complete data base, so there are could be more additional cases of extreme QT prolongation.

The sponsor stated that there were no reports of torsade de pointes or multifocal ventricular tachycardia for the moxifloxacin or comparator treatment group (section 18.3, page 142 of integrated safety summary).

Summary: Moxifloxacin raises the QTc interval in a concentration related manner and therefore, has the potential to cause malignant ventricular arrhythmias, including torsade de pointes, and death. The data

from the NDA indicate that moxifloxacin can cause large increases in QTc (up to 218 msec) at least in some patients.

Recommendation: Moxifloxacin clearly prolongs QTc interval in a concentration-related manner, and, as a result, puts patients at risk for developing malignant arrhythmias. Although the sponsor provides data showing that, on average, moxifloxacin prolongs the QTc about 4 msec, the data did not include all patients treated (about 90% were excluded) and ECG were obtained as late as 6 hours after drug intake (peak concentration is about 2 hours). So the sponsor's argument that moxifloxacin is safe because it only causes a small increase in QTc is flawed. What was shown in the data base is that there are examples of patients on moxifloxacin with changes in QTc intervals greater than 80 msec over baseline with resulting QTc intervals above 500 msec.

While drugs that prolong the QT are not automatically disapproved, it is generally required for such drugs to demonstrate additional benefits compared to other in the same class (or drugs for the same indication) that do not have this adverse effect. If there is a quinolone that provides similar efficacy but does not prolong the QTc (or cause any other serious toxicity not seen with moxifloxacin), it would be difficult to recommend the approval of moxifloxacin.

If moxifloxacin is approved, however, the labeling must state that it is contraindicated in patients with long QT (above 440 msec although this limit can be debated), in patients with a family history of long QT and/or sudden death, in patients already on drugs that prolong the QT, and in patients who had an episode of torsade de pointes with this or any other drug.

In addition, the instructions for use should state that patients taking this drug must have their QTc intervals measured, at maximum drug concentration, periodically during therapy. Those patients with on-therapy QTc increases greater than 15% (this percent increase can be debated) compared to baseline and/or absolute QTc intervals greater than 500 msec (this limit can be debated) should be given alternative treatment.

Finally, a complete understanding of the metabolism and elimination of moxifloxacin as well as QT prolonging potential of metabolites is essential if the drug is approved so dose adjustments can be made. For instance, a lower dose should be considered for females because they tend to have higher mean Cmax and AUC compared to males.

In summary, it is hard to justify approving this agent as first line therapy for non life threating infections in which there are a plethora of treatment choices.

cc
HFD590/RHopkins/MDempsey

APPEARS THIS WAY
ON ORIGINAL