Results of this analysis

Table75: Frequency of ECG events potentially related to QTc prolongation

Table 7 - Frequency of Potentially Relevant QT_c Changes

Treatment Group	Type A1 QT_c Change[1] (No of Events)	Type A2 QT_c Change[1] (No of Events)	Type A3 QT_c Change[1] (No of Events)	Type A4 QT_c Change[1] (No of Events)	Total (No of Patients)
BAY 12-8039 200 mg (N = 37)	0	0	0	0	0 (0%)
BAY 12-8039 400 mg (N = 559)	3	9	9	12	18 (3.2%)
Clarithromycin (N = 136)	0	0	5	0	5 (3.7%)
All comparators[2] (N = 515)	1	2	10	4	14 (2.7%)

Reference: Tables 10.1 (Type A2 changes) and 12.1, Appendix C4

1 See Table 6 for definitions of Types A1, A2, A3 and A4 QT_c events. In Table 12.1, Type A1 is referred to as "Type 2", Type A3 is referred to as "Type 1", and Type A4 is referred to as "Type 3".

2 All comparators including clarithromycin

The analysis of QT intervals excluded patients with other electrocardiographic abnormalities such as multiple ventricular extrasystoles, atrial fibrillation etc. In a broader analysis of ECG abnormalities, these patients were included as shown below.

Table 76: Incidence of electrocardiographic abnormalities by treatment group

Table 8 - Incidence of Other ECG Abnormalities (Post-Dosing ECGs) In Patients With Valid Paired ECGs In All Comparative Studies

	BAY 12-8039 (All)[1] (N = 679)[2]	Clarithromycin (N = 160)[2]	All Comparators[3] (N = 567)[2]
Serious ECG abnormalities (Type B)			
Ventricular tachyarrhythmias	1 (0.15%)	0 (0%)	0 (0%)
Other VPCs	13 (2%)	6 (4%)	10 (2%)
Prolonged QT interval (any)	43 (6%)	11 (7%)	24 (4%)
Other ECG abnormalities (Type C)			
Nonventricular arrhythmias	1 (0.15%)	0 (0%)	0 (0%)
T-wave morphologic changes	34 (5%)	9 (6%)	28 (5%)
Heart block	7 (1%)	5 (3%)	10 (2%)
Infarction or ischemia	29 (4%)	13 (8%)	24 (4%)
Other	23 (3%)	10 (6%)	23 (4%)

Reference: Tables 13.1 and 14.1, Appendix C4. See definition of Type B and C ECG events in Table 6.

1 200 mg and 400 mg patients combined

2 N = all patients at risk

3 All comparator drugs, including clarithromycin

Events classified above as type A, B or C occurred at similar frequencies among Moxifloxacin treated patients, those treated with clarithromycin, and those treated with all comparators including clarithromycin. Moxifloxacin produced more QT prolongations than the pool of comparators, and the only case of a ventricular tachyarrhythmia occurred in a Moxifloxacin treated patient. (See discussion of patients with arrhythmias on page 78).

Clinical events which might indicate an arrythmia were classified according to the liklihood of an association. The classification is provided below.

Table 77: Surrogate events for arrhythmia

Table 9 - Clinical Adverse Events Possibly Associated with QT_c Interval Prolongation

Type	Clinical Adverse Event
Type A	Events consistent with underlying cardiac arrhythmia (potential clinical surrogates of arrhythmia), such as: • Cardiac arrest • Sudden death, of cardiac origin or otherwise • Syncopal episode • Near-syncopal episode • Palpitations • Clinically diagnosed ventricular arrhythmias (no ECG confirmation) • Clinically diagnosed bradyarrhythmia
Type B	Events remotely consistent with underlying arrhythmia, such as: • Serious hypo- or hypertensive episode • Manifestations of myocardial ischemia or injury • Myocardial infarction • Acute CHF and worsening of pre-existing CHF • Circulatory collapse and/or shock • Cerebrovascular event • Other central nervous system event (directly linked to a type A and/or B ECG event) • Psychiatric system event (directly linked to a type A and/or B ECG event described in Table Table 6) • Clinically diagnosed non-ventricular arrhythmia

Sources of the data:
In the worldwide safety database, events considered type A or B were derived from the COSTART directory according to a list of terms.

Table 78: List of Costart terms used as surrogates of arrhythmia

1030040	aggravation reaction
1030200	death
1030780	shock
1030785	sudden death
1090020	chest pain substernal
2010010	Adams Stokes Syndrome
2010030	angina pectoris
2010050	arrhythmia
2010060	atrial arrhythmia
2010070	atrial fibrillation
2010080	atrial flutter
2010100	AV block complete
2010120	AV Block second degree
2010140	bigeminy
2010150	bradycardia
2010170	cardiomegaly
2010180	congestive heart failure
2010230	coronary thrombosis
2010260	electrocardiogram abnormal
2010280	extrasystoles
2010290	heart arrest
2010310	heart failure
2010340	left heart failure
2010350	multifocal extrasystoles
2010370	myocardial infarct
2010390	nodal arrhythmia
2010400	nodal tachycardia
2010410	palpitation
2010480	QT interval prolonged
2010500	sinus bradycardia
2010510	ST depressed
2010520	ST elevated
2010530	supraventricular extrasystoles
2010540	supraventricular tachycardia
2010550	T amplitude decreased
2010560	T inverted
2010570	tachycardia
2010570	tachycardia
2010585	torsades de pointes
2010590	ventricular arrhythmia
2010600	ventricular extrasystoles
2010610	ventricular fibrillation
2010630	ventricular tachycardia
2020020	shock
2030100	cerebral arterial thrombosis
2030130	cerebral infarct
2030140	cerebral ischemia
2030170	cerebrovascular accident
2030260	hypertensive encephalopathy
2030380	myocardial ischemia
2030590	syncope
8020220	cerebral arterial thrombosis
8020230	cerebral embolism
8020250	cerebral cerebral infarct
8020260	cerebral ischemia
8020270	cerebral thrombosis
8020300	cerebrovascular accident

4926 patients treated with Moxifloxacin were included. 4301 patients were treated with moxifloxacin in comparative studies and 3415 were treated with comparator drugs.

Surrogates for arrythmia as described in the above table occurred in 2.4% of all moxifloxacin treated patients, 2.3% of moxifloxacin treated patients participating in controlled trials, and 2% or all comparator treated patients.
The most frequent surrogate event recorded was tachycardia (moxifloxacin 17 patients (0.4%) and comparator 15 patients (0.4%)). Of surrogates, syncope (21/4926 vs 6/3415), angina (10/4926 vs 1/3415) and atrial fibrillation (13/4926 vs 2/3415) were more frequent with Moxifloxacin than comparator. Substernal chest pain was more frequent in comparator groups as shown below:

Table 79: Surrogate clinical events for arrythmia

Clinical Event	All BAY 12-8039-Treated Patients (N = 4926)[2]	All Comparators-Treated Patients[3] (N = 3415)[3]
Body as a whole		
Death[4]	4 (<1%)	2 (<1%)
Aggravation reaction	3 (<1%)	2 (<1%)
Sudden death	1 (<1%)	0 (<1%)
Substernal chest pain	1 (<1%)	5 (<1%)
Cardiovascular system		
Tachycardia	21 (<1%)	15 (<1%)
Syncope	21 (<1%)	6 (<1%)
Atrial fibrillation	13 (<1%)	2 (<1%)
Palpitation	13 (<1%)	9 (<1%)
Angina pectoris	10 (<1%)	1 (<1%)
Congestive heart failure	6 (<1%)	5 (<1%)
Heart failure	5 (<1%)	3 (<1%)
Shock	4 (<1%)	1 (<1%)
Arrhythmia	3 (<1%)	3 (<1%)
Bradycardia -	3 (<1%)	3 (<1%)
Abnormal ECG	3 (<1%)	1 (<1%)
Heart arrest	3 (<1%)	0 (0%)
QT interval prolonged (clinical events)	3 (<1%)	1 (<1%)
Cerebrovascular accident	3 (<1%)	1 (<1%)
Myocardial infarct	2 (<1%)	4 (<1%)
Ventricular fibrillation	2 (<1%)	0 (0%)
Atrial flutter	1 (<1%)	1 (<1%)
Left heart failure	1 (<1%)	0 (0%)
Sinus bradycardia	1 (<1%)	0 (0%)
AV block second degree	0 (0%)	1 (<1%)
Extrasystoles	0 (0%)	1 (<1%)
Supraventricular extrasystoles	1 (<1%)	0 (0%)
Supraventricular tachycardia	1 (<1%)	1 (<1%)
Ventricular arrhythmia	1 (<1%)	0 (0%)
Ventricular extrasystoles	1 (<1%)	1 (<1%)
Ventricular tachycardia	0 (0%)	2 (<1%)
Myocardial ischemia	1 (<1%)	0 (0%)
Nervous system		
Cerebral infarct	1 (<1%)	1 (<1%)
Cerebral ischemia	0 (0%)	2 (<1%)

Reference: Appendix C5, Table 18, A1 and A2.
1 Reported clinical adverse events that were defined as surrogate events for potential underlying cardiac arrhythmia. These events were the Type A and B clinical events (see Table 2) that were mapped to matching COSTART terms.
2 Appendix C5, Table 18 (A1), all BAY 12-8039 patients valid for safety analysis (active-controlled and open studies).
3 Appendix C5, Table 18 (A2), all comparator patients valid for safety analysis (in active-controlled studies).
4 "Death" as an adverse event. Does not include deaths that were not reported as separate adverse events on the case report form (i.e. in instances where only adverse events associated with deaths and not "death" were reported).

MO comment: Despite occurring in less than 1% of treated patients, tachycardia, syncope, palpitation and angina were more common in moxifloxacin patients than control treated patients.

Some of the excess cases of syncope were ascribed to sinus puncture in an uncontrolled study as discussed below.

Thirteen syncopal episodes occurred on the same day as sinus puncture and may have been related to this procedure (11 in a non-comparative study, 1 in a moxifloxacin treated patient in a comparative study and one in a comparator treated patient)

Dose relation:
Any surrogate event occurred in 2.5% of 4370 patients treated with a 400mg dose of moxifloxacin and 2% of 556 patients treated with a 200mg dose of moxifloxacin. The number of patients with adverse events in these two groups was too small to allow a statistically meaningful comparison of doses.

The incidence of any surrogate adverse event regarded as drug related was 1.3% in Moxifloxacin treated patients and 1.2% in comparator treated patients. Drug related surrogate adverse events were equally common in patients treated with 400mg and 200mg of Moxifloxacin (1.3% in each).

Patients with no risk factors for QT prolongation were identified after removing all patients with past cardiac problems or concomitant medication that prolonged the QTc interval as shown below

Table 80: Surrogate events in patients with risk factors for QTc prolongation

RISK GROUP: INDICATION OF PAST CARDIAC PROBLEM AND/OR COMEDICATION KNOWN TO CAUSE QT PROLONGATION

ADVERSE EVENT	ALL BAY 12-8039 (N=1682)	200 MG BAY 12-8039 (N=234)	400 MG BAY 12-8039 (N=1448)
ANY BODY SYSTEM			
ANY EVENT	39 (2%)	5 (2%)	34 (2%)
BODY AS A WHOLE			
ANY EVENT	2 (<1%)	1 (<1%)	1 (<1%)
AGGRAVATION REACTION	1 (<1%)	0 (0%)	1 (<1%)
SUDDEN DEATH	1 (<1%)	1 (<1%)	0 (0%)
CARDIOVASCULAR SYSTEM			
ANY EVENT	37 (2%)	4 (2%)	33 (2%)
TACHYCARDIA	6 (<1%)	1 (<1%)	5 (<1%)
ATRIAL FIBRILLATION	5 (<1%)	1 (<1%)	4 (<1%)
ANGINA PECTORIS	4 (<1%)	0 (0%)	4 (<1%)
SYNCOPE	4 (<1%)	1 (<1%)	3 (<1%)
ELECTROCARDIOGRAM ABNORMAL	3 (<1%)	0 (0%)	3 (<1%)
PALPITATION	3 (<1%)	0 (0%)	3 (<1%)
CONGESTIVE HEART FAILURE	2 (<1%)	0 (0%)	2 (<1%)
CEREBROVASCULAR ACCIDENT	2 (<1%)	0 (0%)	2 (<1%)
ARRHYTHMIA	1 (<1%)	0 (0%)	1 (<1%)
BRADYCARDIA	1 (<1%)	0 (0%)	1 (<1%)
HEART FAILURE	1 (<1%)	0 (0%)	1 (<1%)
LEFT HEART FAILURE	1 (<1%)	0 (0%)	1 (<1%)
MYOCARDIAL INFARCT	1 (<1%)	0 (0%)	1 (<1%)
QT INTERVAL PROLONGED	1 (<1%)	0 (0%)	1 (<1%)
SUPRAVENTRICULAR EXTRASYSTOLES	1 (<1%)	0 (0%)	1 (<1%)
SUPRAVENTRICULAR TACHYCARDIA	1 (<1%)	1 (<1%)	0 (0%)

NOTES: INCIDENCE RATE = # OF EVENTS / # OF PATIENTS, WHERE:
OF EVENTS = # OF PATIENTS REPORTING A DRUG-RELATED EVENT WITH A START DATE DURING OR AFTER TREATMENT.

The patient recorded as a sudden cardiac death was a 75 year old female with CAP and a history of myocardial infarction, CABG and chronic bronchitis. She was found dead one day after completing therapy with Moxifloxacin 200mg QD. Calcium and potassium levels were normal ranging beween 9.3 and 9.1, and 3.9 and 3.4 respectively during therapy. While moxifloxacin cannot be ruled out as a factor in this death, it was noted the patient was treated with a low dose of moxifloxacin, the event occurred a day after therapy had been stopped and the patient suffered from underlying ischeaemic heart disease.

Table 81: Surrogate events in patients without risk factors for QTc prolongation

RISK GROUP: NO INDICATION OF PAST CARDIAC PROBLEM AND NO COMEDICATION KNOWN TO CAUSE QT PROLO

ADVERSE EVENT	ALL BAY 12-8039 (N=3244)	200 MG BAY 12-8039 (N=322)	400 MG BAY 12-8039 (N=2922)
ANY BODY SYSTEM-			
ANY EVENT	24 (<1%)	2 (<1%)	22 (<1%)
BODY AS A WHOLE			
ANY EVENT	4 (<1%)	1 (<1%)	3 (<1%)
DEATH	2 (<1%)	1 (<1%)	1 (<1%)
AGGRAVATION REACTION	1 (<1%)	0 (0%)	1 (<1%)
CHEST PAIN SUBSTERNAL	1 (<1%)	0 (0%)	1 (<1%)
CARDIOVASCULAR SYSTEM			
ANY EVENT	19 (<1%)	0 (0%)	19 (<1%)
TACHYCARDIA	8 (<1%)	0 (0%)	8 (<1%)
PALPITATION	3 (<1%)	0 (0%)	3 (<1%)
SYNCOPE	2 (<1%)	0 (0%)	2 (<1%)
ARRHYTHMIA	1 (<1%)	0 (0%)	1 (<1%)
CONGESTIVE HEART FAILURE	1 (<1%)	0 (0%)	1 (<1%)
QT INTERVAL PROLONGED	1 (<1%)	0 (0%)	1 (<1%)
SINUS BRADYCARDIA	1 (<1%)	0 (0%)	1 (<1%)
VENTRICULAR ARRHYTHMIA	1 (<1%)	0 (0%)	1 (<1%)
VENTRICULAR EXTRASYSTOLES	1 (<1%)	0 (0%)	1 (<1%)
SHOCK	1 (<1%)	0 (0%)	1 (<1%)
NERVOUS SYSTEM			
ANY EVENT	1 (<1%)	1 (<1%)	0 (0%)
CEREBRAL INFARCT	1 (<1%)	1 (<1%)	0 (0%)

NOTES: INCIDENCE RATE = # OF EVENTS / # OF PATIENTS, WHERE:
OF EVENTS = # OF PATIENTS REPORTING A DRUG-RELATED EVENT
WITH A START DATE DURING OR AFTER TREATMENT.

Not unexpectedly, surrogate events were noted to be more common in patients with cardiac risk factors and may have been related to the underlying condition rather than to the drug.

Deaths:
Thirty eight deaths occurred in 8341 (0.46%) valid for safety anlaysis in the global pool. Twenty-eight of these occcured ãmong patients in CAP studies where co-morbidity and severity of illnesss were contributory.

Deaths occurred in 22 of 4926 (0.45%) Moxifloxacin treated patients, 16/4370 patients treated with a 400mg dose and 6/556 treated with a 200mg dose. Deaths occurred in 16 of 3415 (0.47%) control drug treated patients (9 treated with clarithromycin, 6 amoxacillin 1 ofloxacin). An additional death in a clarithromycin treated patientoccurring 41 days after compleiting treatement was excluded form the analysis of deaths as a surrogate for arrhythmia.

Details of patients deaths are listed below illustrating the interval between drug drug therapy and death.

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Table 82: Summary of Deaths in global safety population

Study No. (Indication)	Patient No.	Age (Sex)	Duration of Therapy	Relative Day of Death	Cause of Death
Bay 12-8039 200 mg QD					
112 (CAP)	72	23 (F)	8	+5	Cardio-Respiratory Arrest
119 (CAP)	89	75 (F)	9	+1	Sudden Death, Presumed Cardiac Event
119 (CAP)	228	78 (M)	3	3	Severe Sepsis
119 (CAP)	181	88 (F)	3	+4	Circulatory Failure and Renal Failure
119 (CAP)	785	81 (F)	10	+3	Pulmonary Embolism and Cardiac Arrest
119 (CAP)	548	45 (M)	11	+32	Cardiac Arrest
Bay 12-8039 400 mg QD					
112 (CAP)	67	25 (M)	2	+1	Respiratory Failure - Cardiorespiratory
119 (CAP)	36	75 (M)	9	+51	Laryngeal Carcinoma
119 (CAP)	26	73 (M)	4	+48	Respiratory Failure, Carcinoma Suspected
119 (CAP)	42	74 (M)	4	4	Cardiac Arrest
121 (UTI)	383	76 (M)	8	+19	Prostatic Carcinoma
121 (UTI)	314	87 (M)	5	+7	Aspiration Pneumonia
129 (CAP)	13009	68 (M)	2	+4	Respiratory Arrest
129 (CAP)	25014	76 (M)	2	+13	Ventricular Fibrillation
130 (CAP)	631	57 (F)	12	+13	Narcotic Sedative Overdose
140 (CAP)	10045	73 (M)	9	+33	Hemiplegia
140 (CAP)	10399	72 (M)	9	+52	Ventricular Fibrillation
140 (CAP)	10524	87 (M)	11	11	Cor. Pulmonale, Pulmonary Edema, Ventricular Thrombus
124 (AECB)	126	78 (F)	3	+1	Pneumonia
127 (AECB)	994	79 (M)	11	+36	Acute Pancreatitis
Clarithromycin 500 mg BID					
119 (CAP)	711	75 (F)	8	+2	Acute Renal Failure
119 (CAP)	827	77 (M)	11	+6	Multi-organ Failure
119 (CAP)	416	80 (M)	3	+5	Respiratory Failure
119 (CAP)	92	49 (F)	3	+3	Pneumonia with Abscess and Empyema
119 (CAP)	919	40 (M)	6	+1	Respiratory Failure
119 (CAP)	480[1]	44 (M)	10	+41	Unknown
124 (AECB)	855	55 (M)	8	+16	Infiltrative Carcinoma of the Trachea, Massive Hemorrhage
124 (AECB)	176	72 (F)	2	+1	Myocardial Infarction
127 (AECB)	548	62 (M)	3	+13	Cardiac Arrest
130 (CAP)	958	44 (F)	11	+25	Cerebellar Tumor
Amoxicillin 500 mg TID					
112 (CAP)	41	47 (M)	5	+1	Septicemia
112 (CAP)	114	51 (M)	6	6	Klebsiella Pneumonia
Amoxicillin 1 gm TID					
140 (CAP)	10012	87 (M)	12	+9	High Probability of Pulmonary Embolism
140 (CAP)	10137	43 (M)	4	+3	Cardiac Arythmia
140 (CAP)	10486	42 (M)	4	+1	Cardiorespiratory Insufficiency
140 (CAP)	10242	64 (F)	2	+1	Secondary to Probable Pulmonary Embolism
Ofloxacin 200 mg BID					
121 (UTI)	213	63 (M)	15	+36	Respiratory Failure

1 In addition to the 38 deaths reported in the data pool, one additional death (Patient 480) was reported in a patient who received clarithromycin in Study 0119 and died 41 days after completing treatment.
2 Relative day of therapy or, if preceded by "+", relative days after end of therapy.

Among the moxifloxacin treated patients who died, 4/22 were under 65 years of age, all were on treatment for CAP and none died while receiving Moxifloxacin. Of the remaining elderly patients 3 died while on

treatment. Ventricular fibrillation was listed as a cause of death in a 72 year old male treated for CAP whose death occurred 52 days after completing Moxifloxacin therapy, and in a 76 year old male treated for CAP whose death occurred 13 days following completion of therapy. Cardiac arrest was listed as the cause of death in 4 patients all on treatment for CAP, one of these while receiving Moxifloxacin.

The details of the 4 deaths while on therapy are described below.

- (Study 0119 #228) A 78 year old male with CAP and underlying rheumatoid arthritis, bacteremic with *S aureus* and moraxella species died two days after strating Moxifloxacin 200mg QD. The cause of death was "severe sepsis".
- (Study 0119 #42) A 74 year old male with CAP, severe "respiratory signs" and bilateral infiltrates requiring supplemental oxygen and vasopressors died after 3 days of treatment with Moxifloxacin 400mg QD. The cause of death was respiratory failure.
- (study 0112 #114) A 51 year old male with bacteremia due to *K pneumoniae* died on day 6 of treatment with amoxacillin. The cause of death was pneumonia.
- (study 0140 # 10524) An 87 year old male with CAP, chronic bronchitis and cor pulmonale died on day 11 of therapy with Moxifloxacin 400mg QD. Cause of death was a left ventricular thrombus and pulmonary edema. In this patient, an available ECG during therapy showed a QTc of 442mS.

Eight patients died within one day of completing therapy 3 on Moxifloxacin and 5 on comparator drugs, as described below.

- #89 A 75 year old female with CAP and a history of myocardial infarction, CABG and chronic bronchitis was found dead one day after completing therapy with Moxifloxacin 200mg QD. Calcium and potassium levels were normal ranging beween 9.3 and 9.1, and 3.9 and 3.4 respectively during therapy.
- #67 A 25 year old male with CAP and a unilateral chest infiltrate received one dose of Moxifloxacin 400mg. The drug was withdrawn in favor of IV treatment because of increased respiratory distress and the patient died one day later.
- #126 A 78 year old female died one day after starting alternative antibiotics for AECB. She had received three days of treatment with Moxifloxacin 400mg QD.

The causes of death in the five comparator treated patients dying within one day of completing therapy included; respiratory failure associated with progression of CAP (#919), myocardial infarction in a patient with AECB on day 3 of therapy (#176), septicemia associated with CAP (#41), respiratory failure and sepsis complicating CAP (#10486), and probable pulmonary embolus complicating CAP (#10242). Two of the patients had ECG tracings at baseline, one showing a QTc of 481 mS.

Eleven deaths occurred within 7 days of stopping study drug, 6 on Moxifloxacin and 5 on comparators. Cardiac related deaths were susepcted in 3. One of these patients had a syncopal episode on day 2 and died of a pulmonary embolus 3 days after completing therapy with Moxifloxacin 200mg QD. Among comparator treated patients, two deaths were due to arrhythmia (#10137) and myocardial infarction (#176). The patient with an arrhythmia was recorded as having a QTc of 560mS while on amoxacillin.

Sixteen deaths occurred more than 7 days after completing study drug, most of non-cardiac causes. Late cardiac events were reported in 3 Moxifloxacin treated patients; a cardiac arrest 32 days after therapy, ventricular fibrillation 13 days after therapy and heart failure 22 days after therapy. A 57 year odl female (#631) treated with moxifloxacin 400mg QD with a prolonged QTc of 540mS died of an unrelated narcotic overdose, 13 days after completing therapy.

MO comment: No deaths appeared solely due to the electrocardiographic effects of Moxifloxacin. In all cases, either the time relationship between drug and death, or the underlying medical history suggested that these deaths were not dircectly related to study drug.

Surrogate clinical events occurring in patients with significant QTc changes.

Among the 995 Moxifloxacin treated patients with ECG's included in the "ITT population" 36 patients had Type A QTc changes (see table 74). The table below demonstrates that of these 36 patients, two developed clinical events considered possible surrogates for arrhythmia (tachycardia and a prolonged QTc listed among the clinical events). Among 25 patients treated with comparator drugs who were recorded to have Type A QTc changes, 3 developed type A clinical events, tachycardia in two and arrhythmia in one.).

Table 83: Type A clinical events in patients with Type A QTc changes.

Patient No (Study No)	Age (Sex)	Baseline Qtc[1]	Post-Dosing QTc[1]	Type A Clinical Events
BAY 12-8039-treated patients (all patients with paired valid ECGs in all studies)				
252 (128)	56 (M)	437	469	None
630 (128)	73 (M)	413	451	None
616 (119)	59 (M)	406	451	None
618 (124)	74 (M)	400	455	None
901 (124)	62 (M)	331	438	None
58 (127)	63 (M)	445	479	None
882 (127)	51 (F)	400	466	None
1047 (127)	83 (M)	415	465	None
766 (128)	62 (M)	464	500	None
597 (128)	35 (M)	389	449	None
725 (128)	87 (M)	414	454	None
8034 (129)	42 (F)	396	461	None
631 ((130)	57 (F)	374	438	None
635 (130)	35 (F)	372	431	None
10074 (140)	65 (F)	334	419	None
10046 (140)	72 (F)	452	519	None
10248 (140)	67 (F)	225	465	None
10255 (140)	82 (M)	417	498	None
10258 (140)	21 (M)	348	406	None
10270 (140)	23 (M)	418	453	None
10533 (140)	54 (M)	390	455	None
10544 (140)	60 (F)	365	583	Tachycardia
10500 (140)	27 (M)	420	452	None
10669 (140)	38 (M)	439	535	None
10757 (140)	26 (F)	356	423	None
10342 (140)	87 (F)	388	457	None
10365 (140)	53 (M)	437	492	Prolonged QT interval[2]
10368 (140)	27 (F)	363	472	None
10390 (140)	42 (M)	319	373	None
14026 (158)	60 (M)	433	463	None
21023 (158)	31 (M)	411	450	None
40001 (158)	52 (M)	416	454	None
28001 (1610	37 (F)	367	479	None
31002 (161)	42 (F)	345	452	None
37003 (161)	45 (F)	442	483	None
37016 (161)	37 (F)	342	424	None
All clarithromycin-treated patients				
927 (124)	67 (F)	458	492	None
614 (124)	38 (M)	427	459	None
817 (127)	52 (M)	416	450	None
561 (127)	56 (F)	415	471	None
487 (130)	36 (M)	423	454	None
All patients treated with other comparative drugs				
339 (118)	24 (F)	372	435	None
49 (121)	70 (M)	425	495	Tachycardia
443 (121)	65 (M)	391	456	None

164 (131)	63 (F)	369	435	None
154 (131)	70 (M)	432	472	None
10137 (140)	43 (M)	402	458	Arrhythmia
10138 (140)	66 (M)	413	466	Tachycardia
10173 (140)	27 (F)	349	414	None
10553 (140)	86 (F)	341	415	None
10347 (140)	69 (M)	456	495	None
10063 (140)	72 (M)	376	436	None
10344 (140)	47 (F)	367	512	None
10502 (140)	59 (M)	494	536	None
10145 (140)	80 (M)	419	452	None
10691 (140)	19 (M)	343	424	None
34001 (161)	26 (F)	342	415	None
36025 (161)	49 (F)	364	423	None
37004 (161)	57 (F)	522	593	None
37019 (161)	28 (F)	340	394	None
37021 (161)	59 (F)	438	471	None

Reference: Appendices E (excluding patients with negative delta QT_c) and F. Post-dosing QTc hand-tabulated from change in QTc and baseline QTc.
1 In milliseconds
2 Listed in database as clinical event not as ECG event

MO comment: No consistent association was seen between Type A electrocardiographic changes and type A surrogate clinical events for arrhythmia, either in Moxifloxacin or comparator treated patients.

Arrhythmias.

Treatment emergent ventricular arrhythmias were reported in 4/4926 (0.08%) Moxifloxacin treated patients (ventricular arrhythmia (1), ventricular fibrillation (2) ventricular tachycardia (1) compared with 3/3415 (0.09%) of comparator treated patients.
ECGs were available on 3 of the 4 moxifloxacin treated patients with ventricular arrhythmic events. One did not have a calculated QTc, and one had a baseline QTc only, of 402mS. The remaining patient was a 72 year old man with atrial fibrillation and a baseline QTc of 401mS. (He was excluded from the ITT ECG evaluation because of atrial fibrillation.) He developed a post-dosing QTc of 465mS and ventricular fibrillation was reported 52 days after the last dose of study drug. Concomitant medications included enalapril, isosorbide, digoxin and aspirin.

MO comment: The long time interval between study drug administration and ventricular fibrillation in this patient makes a causal relationship unlikely.

Of the 3 comparator treated patients with ventricualr arrhythmic events, QTc data was availble for one. In this 92 year old patient with extrasystoles, non-sustained ventricular tachycardia (excluded from the ITT analysis on this basis) had a baseline calculated QTc of 439mS and a post-dosing QTc of 479mS.

Arrhythmias (type not specified on the adverse event report)
Treatment emergent events recorded as "arrhythmia" were reported in 3/4926 (0.06%) Moxifloxacin treated patients valid for safety evaluation compared with 3/3415 (0.08%) comparator treated patients..
ECG results available for one of the three Moxifloxacin treated patients, an 81 year old woman, showed a baseline QTc of 443 mS and a post dosing QTc of 394mS
ECG data were available for two of the comparator treated patients with arrhythmias.One (#10486 study 140, a 42 year old male with CAP) had a baseline QTc of 481 and no post dosing ECG. The other (#10137 study 140, a 43 year old man treated with amoxacillin) had a baseline QTc of 402mS and a post dosing QTc of 458mS.

Selected subpopulation analyses were performed targeting individuals possibly more prone to arrhythmias:

Gender effect

In each of the four global ECG datasets, women showed a larger change in QTc than men. Despite this, "Type A" clinical events were no more frequent in women than men. In comparator treated patients, there was no consistent difference in the responses between men and women.

Table 84: Gender differences in mean, maximum and minimum change of QTc (mS)

	Males				Females			
	n	ΔMean QTc	Min QTc	Max QTc	N	ΔMean QTc	Min QTc	Max QTc
Moxi-floxacin (all)	277	0.003	-0.175	0.096	319	0.005	-0.135	0.218
Clarith-romycin	68	0.002	-0.067	0.041	68	0.002	-0.077	0.056
All comp-arators	249	0.000	-0.079	0.08	266	0.000	-0.181	0.063

MO comment: Gender differences for the mean change in QTc were similar. However the maximum change among females was 0.218mS compared with 0.096mS in males. Maximum changes among patients treated with comparator drugs were smaller. The data suggests that female outliers may be more likely to develop significant QTc prolongation on Moxifloxacin than males, though more data would be required to confirm this statistically.

The effect of age on the degree of QTc prolongation is shown below for patients with "paired valid ECGs".

Table 85: Age effect on change in QTc for patients with "paired valid ECG's

	N	<30mS	≥30-60mS	≥60mS
<65 years	475	417 (88%)	52 (11%)	6 (1%)
≥65-<75	83	72 (87%)	9 (11%)	2 (2%)
≥75 years	53	49 (92%)	3 (6%)	1 (2%)

MO comment: Changes in QTc ≥60mS were marginally more frequent in patients older than 65 years compared to younger patients, however the number of elderly patients studied was relatively small.

Dose relationship
Although the mean QTc prolongation was similar for patients with paired valid ECGs given Moxifloxacin 400mg or 200mg, the maximum change was higher in the 400mg group (0.218 sec versus 0.041 sec).

Effects of Hypokalemia/hypocalcemia
Hypokalemia was identified if the baseline serum potassium was <3.5mEq/l and hypocalcemia if the serum calcium was less than 8.5mg/dL.
Electrolyte changes were evaluated for their effect on QTc change as shown below.

Table 86: Effect of baseline electrolyte abnormalities on change in QTc (from Table 10.1 7-1458)

		<30mS	>=30-60mS	>=60mS
Moxifloxacin (all)	hypokalemia and hypocalcemia absent	484/535 90.4%	46/535 8.6%	5/535 0.9%
	hypokalemia or hypocalcemia present	42/59 71.2%	14/59 23.7%	3/59 5.1%
Comparator (all)	hypokalemia and hypocalcemia absent	423/461 91.8%	36/461 7.8%	2/461 0.5%
	hypokalemia or hypocalcemia present	42/50 84%	8/50 16%	0/50 0%

MO Comment: Hypokalemia or hypocalcemia had a marked effect on the proportion of patients developing significant increases in QTc with Moxifloxacin treatment. QTc changes ≥60mS occurred in 5.1% of patients with electrolyte abnormalities compared with 0.9% of patients with normal electrolytes. This trend was not observed among patients treated with comparator drugs.

A similar analysis was performed to examine the effect of hypokalemia alone as shown below:

Table 87: Effect of hypokalemia on QTc prolongation

Delta QTc 30-60mS		
	Moxiflox	Comparator
K >=3.5	12.1 % (147/1211)	8% (84/1044)
K < 3.5	18.9% (7/37)	7.3% (3/41)

Delta QTc >60		
	Moxiflox	Comparator
K >=3.5	1.7% (20/1211)	1.1% (12/1044)
K < 3.5	8.1% (3/37) p=0.002	0% (0/41)

MO comment: Hypokalemia was significantly associated with prolongations of the QTc interval >60mS

A history of cardiac conditions predisposing to a prolonged QTc interval (congenital or acquired QTc prolongation, bradycardia, CHF, reduced LVEF and a history of symptomatic arrhythmia) was elicited for a relatively small number of patients and appeared not to influence the change in QTc on treatment as shown below.

Table 88: Influence of predisposing cardiological factors on changes in QTc interval. Among all patients with paired valid ECG's, patients with an ICD-9 code for underlying cardiac disease were identified.

Predisposing Factors	< 30 msec N (%)[2]	≥ 30-60 msec N (%)[2]	≥60 msec N (%)[2]
No	548 (96%)	66 (99%)	9 (100%)
Yes	24 (4%)	1 (1%)	0 (0%)

MO comment: Since a prospective cardiological assessment was not perfomed on study participants, a substantial number of baseline abnormalities might not have been recorded redendering the above analysis unreliable.

Effect of concomitant medications on QTc prolongation
Concurrent treatment with the following medications was examined for an effect on the change in QTc interval: Class 1A and III antiarrhythmic agents, phenothiazines, non-sedating antihistaminics, potassium wasting diuretics and mineralocorticoids. There did not appear to be an effect of these medications on the QTc changes following treatment with Moxifloxacin as shown below.

Table 89: Effect of concomitant medications on QTc changes during treatment with Moxifloxacin (population with paired valid ECG's)

Concomitant Medication[1]	< 30 msec N (%)[2]	≥ 30-60 msec N (%)[2]	≥60 msec N (%)[2]
Yes	215 (38%)	25 (37%)	3 (33%)
No	357 (62%)	42 (63%)	6 (67%)

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Review of 4 month safety update:

This supplement incorporates new safety data on 263 patients treated with 400mg QD of moxifloxacin for 10 days and 275 control patients assigned to receive cefuroxine for 10 days, who participated in sinusitis study 100107. These data were obtained between the "lock date" for the NDA (Sept 10,1998) and the lock date for this safety update (Dec 31, 1998).
Additional information supplied in this update includes narratives for premature discontinuations due to adverse events, serious adverse events and deaths for the 4 ongoing studies detailed below.

Table 90: Ongoing studies

Study	Indication	Study type	Dose of Moxi	Duration of Rx
100131	Acute sinusitis	Open uncontrolled (US & Canada)	400mg QD	10 days
100160	AECB	Double blind vs azithromcyin (US & Canada)	400mg QD	5 days
100161	Acute sinusitis	Double blind vs trovafloxacin	400mg QD	10 days
0134	Pyelonephritis	Double blind vs ofloxacin (Europe)	400mg QD	

Following incorporation of the additional 263 patients among the population valid for safety analysis in the NDA, there were no significant changes in the rates for adverse events as shown below.

Table 91: comparison of adverse event rates for NDA and updated safety populations

	NDA	Updated safety population
At least one AE	46%	47%
Drug related AEs	32%	32%
Digestive	19%	19%
Deaths	0.45%	0.42%*
Discontinuations due to AEs	5%	5%
Drug related discontinuations	4%	4%
Serious Adverse events	4%	4%

*No new deaths were reported in the 4 month safety update
One new serious adverse event listed "chest pain unrelated to the drug" was reported in the update.
The laboratory findings among controlled studies before and after the 4 month safety update are shown below.

Table 92: Laboratory findings: comparison of NDA and updated databases for all patients valid for safety analysis (moxifloxacin doses between 200 and 400mg QD).

	NDA	Updated safety population
High prothrombin time	13%	14%
High abs eosinophil count	10%	12%
Elevated chloride	15%	16%
Low abs neutrophil count	9%	11%

Cardiac safety

The safety data added to the database as a result of inclusion of study 100107 are shown below:

Table 93: Number of patients added to each safety population as a result of inclusion of study 100107. Combination of NDA and updated patient numbers are listed in parentheses.

	Moxifloxacin 400mg QD	Comparator (cefuroxime)	Total
Valid for safety	263	274	537
ECG's ITT population	242 (1067)	257	499
ECGs Paired valid	228 (787)	244	472

When incorporating the data included in the 4 month safety update (which now included sinusitis study 100107 where paired ECGs were obtained on all patients, the calculated mean change in QTc on treatment increased as shown below:

Table 94: Comparison of mean changes in the QTc for worldwide NDA safety populations treated with 400mg moxifloxacin, before and after inclusion of 4 month safety update.

	ITT (NDA) [95%CI]	ITT (Updated)	Valid paired (NDA)	Valid paired (updated)
Mean change in QTc	5 [3-7]	6 [5 to 8]	5 [3-7]	7 [5 to 8]

There were no new patients in study 100107 with treatment emergent QTc >500mS. One of the comparator treated patients in this study had a baseline QTc>500mS and an on treatment QTc of <500mS

Treatment emergent changes in the QTc of >60mS occurred in 2/228 patients in the "paired valid" populuation who were treated with moxifloxacin 400mg. For this population, treatment emergent changes of 30-60mS occurred in 31/228 patients. Comparable figures for comparator treated patients were 0/244 and 16/244 respectively.

The mean changes of the QTc for patients in study 100107 are shown below.

Table 95: Mean changes in QTc for patients in study 100107

	ITT population		Paired valid ecg population	
	N	Mean ΔQTc [95%CI]	N	Mean ΔQTc [95%CI]
Moxifloxacin 400mg X 10 days	242	12 [10-14]	228	12 [9-14]
Comparator (cefuroxime)	257	2 [0-4]	244	2 [0-5]

The marked difference was noted between the mean QTc prolongation in study 100107 when compared with the NDA data for patients treated with moxifloxacin 400mg. Patients treated with comparator agents showed much smaller differences when the two datasets were compared.

In an attempt to understand this difference, baseline characteristics of the patients in study 100107 were compared with those of patients included in the original NDA. These characteristics are described in the table below.

Table 96: baseline characteristics of ITT populations in datasets from the NDA and from study 100107

	NDA dataset [n=919]	Study 100107 [n=242]
Mean age (+/-SD)	49.8 (+/- 17.5)	39.8 (+/- 13.4)
mean body weight (+/-SD) kg	76.3 (+/-19.5)	81 (+/- 20.7)
Baseline Heart rate (+/-SD)	80.8(+/-17.1)	71.6 (+/-11.4)
% female	53	62
% with underlying cardiac condition	4.8	1.7
% on concomitant medication affecting QT interval	37	24

MO comment: Participants in study 100107 were on average younger, heavier, and less likely to have underlying cardiac disease or to be on concomitant medications known to prolong the QTc interval. All these factors should if anything reduce any prolongation of the QTc. The slight preponderance of females and of slower-heart rates in study 100107 does not appear significant enough to explain the observed differences in ΔQTc between the two populations. The fact that comparator treated subjects did not show a substantial difference in ΔQTc between the two populations supports the notion that both populations had similar baseline characteristics.
Notably, in study 100107, 93% of patients valid for safety were included in the ITT population for ECG evaluation and 88% were included in the "Valid paired ECG" population. In the NDA only 53% of patients with ECGs were eligible for the "valid paired ECG population". Since paired ECG's were required from the beginning of this study (unlike other studies in the NDA) it is possible that more rigorous attention was paid to the timing of ECG's in this study and they may more closely approximate the time of C max.

The baseline distributions of QTc intervals for both populations were similar.

Eight new clinical surrogate events for arrhythmia were reported in the 4 month safety update, five among patients treated with moxifloxacin and 3 among patients treated with cefuroxime as described in the table below:

Table 97: Surrogate events for arrhythmia in study 100107

Patient #	Drug	Event	ΔQTc mS (maximum QTc)
42001	Moxifloxacin	Tachycardia	+10
42015	Moxifloxacin	Tachycardia	+20
48004	Moxifloxacin	Tachycardia	-20
27026	Moxifloxacin	Syncope	+40 (440 on Rx)
	Moxifloxacin	Visual QT prolongation	+70 (480 on Rx)
42017	Cefuroxime	Syncope	-30
8097	Cefuroxime	Syncope	-10
13007	Cefuroxime	ST depression	+10

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Summary and conclusions:

The safety concerns with this product have been dominated by the effect of Moxifloxacin in prolonging the QT interval of the electrocardiogram. In vitro data suggest that Moxifloxacin weakly inhibits the Ikr ionic channel in mouse atrial cells. Animal data confirm the ability of moxifloxacin to cause a dose related increase in the QTc interval. At doses comparably more than 70 times the human mg/kg dose, ventricular arrhythmias and torsade de pointes were seen. In human studies, increases in the QTc occur with rising serum concentrations. Linear regression lines relating QTc prolongation to serum concentration have shallow slopes ranging between .0056 and .0061mS/µg/l. From in vitro experiments and a study examining the effects of moxifloxacin on theophylline pharmacokinetics it appears that moxifloxacin is not appreciably metabolized by the p450 enzyme system. Thus the potential for increased cardio-toxicity as a result of this type of drug interaction (with a considerable impact on other products such as [redacted] is reduced.

In broader clinical studies where timing and quality of electrocardiographic data has been less rigorous, single oral 400mg doses of moxifloxacin cause a mean prolongation of the QTc interval at the presumed time of Cmax of approximately 7mS (compared with 0-2 mS in comparator treated patients). In one study of 228 patients with sinusitis, this value was as high as 12 mS.
Significant outliers, defined as those with treatment emergent changes in the QTc of 60mS or more, or QTc values >500mS after treatment were significantly more common among moxifloxacin treated patients than those treated with comparator agents (11/839 [1.3%] vs 2/759 [0.3%]). However when clinical events suggesting treatment related ventricular arrhythmias were sought, the few reported cases were neither more frequent nor more suspicious of drug toxicity than those occurring in comparator treated patients.
A paucity of data on the effects of continuous dosing, and administration of doses in excess of those recommended has limited our ability to establish a confident safety margin for the use of the product, and these aspects will require further investigation as part of a phase 4 study program. The QTc prolonging effects of moxifloxacin are aggravated by hypokalemia. Other conditions that may theoretically increase the risk of QT prolongation include congenital prolongations of the QTc, concurrent use of other drugs prolonging the QT interval and low magnesium levels in the blood.

With the size of the available database, the risk of ventricular arrhythmias cannot be determined. Judged by the lack of conclusive event rates in the database, and post marketing event rates for ventricular arrhythmias among other quinolones with similar effects on the QT interval (Sparfloxacin, Grepafloxacin) tens of thousands of treatment courses will be required to estimate this risk. Given this uncertainty, moxifloxacin should only be used where the perceived benefit exceeds the risk. Surveillance of post marketing adverse event reports will be needed to monitor the cardiac safety of the product in the general population.

Experience with moxifloxacin tablets in more than 4000 patients has revealed a clinical profile of predominantly gastro-intestinal drug-related adverse events including nausea (8%) and diarrhea (7%). Central nervous system toxicity has been infrequent, and dizziness (3%) has been the most common complaint. Cardiac toxicity other than that discussed above, was not evident apart from an unexplained increase in the number of patients with atrial fibrillation who were treated with moxifloxacin compared with comparator agents. Phototoxicity, liver toxicity and hypoglycemia were neither more frequent nor more severe than seen using comparator agents. Cases of tendon rupture were not reported. Among abnormal laboratory findings, moxifloxacin was shown to produce more anemia and more prolongations of the prothrombin time. There was no evidence of a haemolytic syndrome and these laboratory abnormalities appeared not to result in clinical sequelae.

While the safety of moxifloxacin appears comparable to some marketed quinolones, the full extent of toxicity in large numbers of patients among the general population cannot be predicted. Warnings in the label and post marketing surveillance and phase 4 studies will be used to address this issue.

Phase 4 recommendations:

[redacted]

- Additional human studies using double the recommended dose of moxifloxacin should be performed to further characterize the spectrum of electrocardiographic safety.
- Additional human studies using continuous dosing for at least 2 weeks should be performed correlating effects on the QTc interval with steady state blood levels of the drug.

/S/

Leonard V Sacks, M.D.
Medical officer, DSPIDP

Concurrence
HFD590/MTL/HopkinsR

CC:
NDA 21-085
HFD-590/DivDir/GoldbergerM /S/
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

Medical Officer's Review of Acute Sinusitis Indication for NDA # 21-085
AVELOX™ (moxifloxacin hydrochloride) Tablets

Table of Contents **Page**

I. Executive Summary

Moxifloxacin hydrochloride (also referred to as BAY 12-8039) is a new synthetic broad spectrum C-8-methoxy-fluoroquinolone under development by the Bayer Corporation. The sponsor asserts in the NDA cover letter that moxifloxacin "represents a significant improvement over currently available fluoroquinolones due to its improved activity against difficult-to-treat organisms and pathogens that have been showing increasing resistance to many beta-lactams as well as other antibiotic drug classes." The NDA contains numerous large, controlled, multicenter, multinational clinical trials to demonstrate the efficacy and safety of this new antimicrobial agent for the following indications: acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia,

The proposed indication for acute sinusitis in the NDA submission reads as follows:

> **Acute Sinusitis** caused by *Streptococcus pneumoniae* (including penicillin susceptible, intermediate and resistant strains). *Haemophilus influenzae*, or *Moraxella catarrhalis*.

The proposed dosage and duration of therapy in the original NDA submission was 400 mg orally every 24 hours for 7-10 days. Since the original submission the sponsor has indicated that they will revise the proposed duration of therapy to a full 10 days.

The following five pivotal studies were submitted in support of the acute bacterial sinusitis indication (modified by MO from NDA Volume 2, page 28):

Protocol #/ Country	Status	Trial Design	Treatment/Dose	Duration of Treatment	# Patients /Treatment Arm (Total)
#100107 US	Completed	controlled, double blind, parallel group, randomized Phase III	Cefuroxime Axetil 250 mg BID x 10 days BAY 12-8039 400 mg QD x 10 days	10 days 10 days	275 267 (542)
#0161 SF, F, D, GR, IL, LT, GB	Completed	controlled, double blind, parallel group, randomized Phase III	BAY 12-8039 400 mg QD x 10 days Cefuroxime Axetil 250 mg BID x 10 days	10 days 10 days	246 251 (497)
#0116 D, E, F, GR, IL, S, SF	Completed	controlled, double blind, parallel group, randomized Phase III	BAY 12-8039 400 mg QD x 7 days Cefuroxime Axetil 250 mg BID x 10 days	7 days 10 days	244 254 (498)
D96-023 US	Completed	uncontrolled, open label, -, non-randomized Phase III	BAY 12-8039 400 mg QD x 7 days	7 days	372 (372)
D96-024 US, CA	Completed	controlled, double blind, parallel group, randomized Phase III	BAY 12-8039 400 mg QD x 7 days Cefuroxime Axetil 250 mg BID x 10 days	7 days 10 days	238 233 (471)

M/F = male/female; B/W/O = black, white, other; QD = once daily; BID = twice daily
CA = Canada; D = Germany; E = Spain; EST = Estonia; F = France; GB = Great Britain; GR = Greece; IL = Israel; LT = Lithuania; S = Sweden; SF = Finland;
US = United States

The five studies were generally similar in design. Protocol inclusion criteria required baseline radiographic evidence of infection and the presence of at least two of the following symptoms associated with acute maxillary sinusitis: nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar pain/tenderness and purulent nasal discharge. A further requirement for symptom duration less than 28 days lessened the likelihood of enrolling patients with chronic sinusitis. However, only Study 100107 required symptom duration of at least 7 days (as recommended by the draft DAIDP evaluability criteria guidance document for acute sinusitis) to minimize enrollment of patients with viral upper respiratory tract infections. In all studies, moxifloxacin was administered as a single 400 mg oral daily dose for either 7 or 10 days. Patient assessments as outlined in the protocols were performed at baseline (within 48 hours before dosing), during the study (ranging from Day 2 to Day 9 of therapy), post-therapy (ranging from 4-14 days following therapy) and at a final follow-up visit (27-31 days following therapy). While microbiological efficacy data were gathered in Studies 0161, 0116 and D96-023, only the latter study used the antral puncture technique to obtain all isolates. Since antral puncture is the only currently FDA-accepted means of documenting microbial etiology of sinus infections, Study D96-023 was designed to demonstrate bacteriological efficacy of moxifloxacin against the bacterial pathogens which commonly cause sinus infections.

The sponsor used the following time windows to assess the test of cure for the various studies in the final efficacy analyses:

Study	Test of Cure Window (No. of Days Post-Therapy)
100107	7-14
0161	4-7
0116	4
D96-023	21-37
D96-024	21-37

The FDA medical reviewer analyses used the final followup visit (27-31 days post-therapy) for test of cure visit in all studies. Clinical response at this visit was documented in all studies and allowed sufficient time off therapy (greater than 1 week) to assess clinical response. Use of the same test of cure visit across all studies also allowed for easier comparison of efficacy results among the studies.

The following two tables summarize the clinical efficacy data for the clinically evaluable and all-treated patients populations according to the sponsor and the FDA medical officer analyses, respectively:

Clinical Efficacy of Moxifloxacin and Comparators in Acute Sinusitis (per Sponsor)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.*	All-Treated Patients Efficacy Rate	95% C.I.**
100107	Moxifloxacin	90% (200/223)	(-5.1, 6.1%)	89% (210/235)	(-5.1%, 6.1%)
	Cefuroxime	89% (209/234)		89% (219/246)	
0161	Moxifloxacin	94% (203/217)	(-5.5%,3.4%)	91% (222/245)	(-5.2%, 4.8%)
	Cefuroxime	95% (210/222)		91% (228/251)	
0116	Moxifloxacin	97% (204/211)	(1.5%, 10.6%)	89% (216/242)	(-3.7%, 7.8%)
	Cefuroxime	91% (204/225)		87% (219/251)	
D96-023	Moxifloxacin	80% (270/336)	(76%, 84%)	81% (289/357)	(77%, 85%)
D96-024	Moxifloxacin	81% (154/191)	(-17.1%, -3.8%)	81% (164/203)	(-17.2%, -4.3%)
	Cefuroxime	91% (176/193)		92% (187/204)	

*Excludes patients with indeterminate clinical response at the test of cure visit.

**95% confidence interval (C.I.) refers to point estimate for gatifloxacin efficacy rate in Study D96-023 and refers to the difference in efficacy rates for the remaining studies

Clinical Efficacy of Moxifloxacin and Comparators in Acute Sinusitis (per Medical Officer)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.*
100107	Moxifloxacin	89% (193/217)	(-0.4%, 13.3%)
	Cefuroxime	83% (188/228)	
0161	Moxifloxacin	87% (183/210)	(-8.3%, 5.0%)
	Cefuroxime	89% (190/214)	
0116	Moxifloxacin	87% (180/207)	(-1.6%, 13.2%)
	Cefuroxime	81% (177/218)	
D96-023	Moxifloxacin	76% (253/331)	(72%, 81%)
D96-024	Moxifloxacin	75.1% (139/185)	(-21.8%, -5.3%)
	Cefuroxime	88.7% (165/186)	

*95% confidence interval (C.I.) refers to point estimate for gatifloxacin efficacy rate in Study D96-023 and refers to the difference in efficacy rates for the remaining studies

In general, the moxifloxacin efficacy rates at the test of cure visit were near or above 80% in clinically evaluable patients. The response rate of 76% in the FDA analysis for the clinically evaluable moxifloxacin patient population in Study 0116 may have resulted from enrollment of patients with more severe infections in this study or may have related to the open-label design of this study.

Of note, studies 0116 and D96-024 showed strikingly disparate efficacy results for the seven-day moxifloxacin treatment regimen. The 95% confidence interval for the difference in efficacy rates between the treatment arms in Study 0116 suggests the superiority of moxifloxacin over the 10-day course of cefuroxime. However, the 7-day moxifloxacin regime failed to meet protocol-specified criteria for clinical equivalence to the same cefuroxime regimen in Study D96-024. Since the two other comparator-controlled trials in the NDA showed clinical equivalence of the ten-day moxifloxacin regimen to cefuroxime, the lower efficacy rates for moxifloxacin in Study D96-024 may have resulted from insufficient duration of treatment. Indeed, the current medical literature recommends a minimum of 10 days of antimicrobial therapy for acute sinusitis infections[7]. Hence, the conflicting data presented in the NDA do not convincingly support approval of the 7-day moxifloxacin regimen for the acute sinusitis indication.

Study D96-023 was designed to provide evidence of bacteriological efficacy against the three major pathogens in acute sinusitis: *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* A total of 372 patients were enrolled in the study yielding 74 microbiologically evaluable patients for these pathogens. The overall bacteriological eradication rate for the microbiologically evaluable patients was 86 % (64/74). Eradication rates for *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* were 97% (29/30) and 80% (24/30), and 83% (15/18), respectively. According to the DAIDP Points to Consider Document, the NDA should demonstrate activity against approximately 25 isolates of *S. pneumoniae* and *H. influenzae,* and 15 isolates of *M. catarrhalis* to support an acute sinusitis indication. Thus, the microbiological efficacy data from this study would supports labeling for *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* The medical officer's analysis of the datasets showed 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* to be 100% (6/6) and 88.9% (8/9), respectively. The small number of resistant and intermediate-susceptibility pneumococcal isolates obtained in this study limit the interpretation of these bacteriological efficacy rates and are insufficient to support labeling of these organisms.

The safety profile within the NDA pivotal trials is based on a total of 1355 patients exposed to gatifloxacin. The most commonly reported drug-related adverse clinical events were mild in severity and related to the gastrointestinal tract (nausea, diarrhea, vomiting, dyspepsia, and abdominal pain). Drug-related dizziness was uncommonly reported in studies ($\leq$ 5% of patients), but was generally slightly higher in the moxifloxacin-treated patients compared to those receiving cefuroxime. The effects of moxifloxacin on clinical laboratory values in patients with normal baseline values were generally uncommon, transient and required no specific treatment intervention. In particular, effects on liver function tests were typically mild and either of similar or lesser severity than the approved comparator agent. Only one moxifloxacin patient discontinued from the studies due to a slight worsening of abnormal baseline liver function tests. These abnormal test results had already begun reverting toward normal values prior to cessation of study drug and subsequently normalized within 4 days. Refer

to the integrated safety summary for the NDA (Dr. Leonard Sacks) for further analysis and discussion of the safety database.

In conclusion, the medical officer recommends approval of the ten-day treatment regimen of moxifloxacin for the treatment of acute sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Insufficient data were presented in the sinusitis section of the NDA to support labeling of acute sinus infections due to penicillin-resistant or intermediate susceptibility strains of *Streptococcus pneumoniae*. Following CIPRO® and LEVAQUIN®, gatifloxacin would represent the third fluoroquinolone antimicrobial agent approved by FDA for this indication (see APPENDIX VI)

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II. Study No. 100107: "Prospective, Randomized, Double-Blind, Comparison of the Safety and Efficacy of BAY 12-8039 400 mg QD for 10 Days Versus Cefuroxime Axetil 250 mg BID for 10 Days for the Treatment of Patients with Acute Bacterial Maxillary Sinusitis"

A. Overview

1. Objectives:

This clinical trial was designed to compare the safety and efficacy of BAY 12-8039 400 mg once daily for 10 days versus cefuroxime axetil 250 mg BID for 10 days in the treatment of adult patients with documented acute bacterial maxillary sinusitis.

MO Comment: The FDA approved indication for the comparator agent used in this clinical trial reads as follows:

"Acute Bacterial Maxillary Sinusitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* [redacted] (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."

Ideally, the comparator agent for a pivotal clinical trial would have demonstrated activity against the all three of the "major" pathogens in acute bacterial sinusitis. However, the dosage, frequency and duration of CEFTIN therapy are consistent with the approved labeling for acute sinusitis.

2. Design

This was a prospective, randomized, multicenter, double-blind, Phase III clinical trial comparing the efficacy and safety of BAY 12-8039 400 mg PO once daily for 10 days with cefuroxime axetil 250 mg PO BID for 10 days in the treatment of outpatients with acute, bacterial, maxillary sinus infection.

3. Inclusion Criteria:

Outpatient males or females 18 years of age or older were enrolled if they had a suspected acute maxillary sinus infection as evidenced by radiological paranasal sinus x-ray [redacted] revealing either air-fluid levels, opacification, or ≥6 mm mucosal thickening, and at least 2 of the following findings referable to the sinus infection:

- Nasal congestion
- Post-nasal drainage

- Frequent coughing or throat clearing
- Frontal headache
- Malar tenderness/pain
- Purulent nasal discharge

Only patients presenting with acute signs and symptoms that had been present for more than 7 days but less than 28 days were eligible for study enrollment. Patients who had 2 episodes or less of clinically documented sinusitis during the 12 months prior to screening were also included.

Women of childbearing potential, including women less than one year post-menopausal and/or not surgically sterilized, had to use reliable methods of contraception or abstinence during exposure to study drug. Patients taking oral contraceptives were also to use barrier contraception or abstinence during study drug exposure, since the effect of (BAY 12-8039) on the efficacy of oral contraceptives had not been studied at that time.

MO Comments:

- **The radiographic inclusion criteria are acceptable.**
- **The draft FDA Evaluability Criteria Guidance guidance document for acute sinusitis states that diagnostic signs and symptoms for documentation "should include facial pain/pressure/tightness typically over the maxillary sinuses and periorbital region, a purulent anterior or posterior nasal discharge, nasal congestion, and cough." The sponsor's proposed criteria require only two out of six specified symptoms. The first three of these symptoms (nasal congestion, post-nasal drainage, and frequent coughing or throat clearing) are non-specific for acute bacterial infection and are also manifestations of viral upper respiratory infection (URI) or allergic rhinitis. Thus, the inclusion criteria as defined above may have allowed inclusion of some patients with an allergic or viral rather than an infectious bacterial etiology for their symptoms. Unfortunately, radiographic abnormalities may be present in viral URI as well as in acute sinusitis[1].**

4. Exclusion Criteria:

Patients who had the following were not enrolled:

- A 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 were also excluded
- Inability to take oral medication
- Received systemic antimicrobial therapy within 24 hours prior to enrollment unless the patient was a clinical failure.

- Had past sinus surgery (antral sinus puncture would not be considered sinus surgery)
- A requirement for concomitant systemic antimicrobial therapy with agents not specified in the protocol
- A history of chronic sinusitis, greater than 4 weeks of continuous symptomatology or greater than 2 episodes of clinically documented sinusitis within the previous 12 months
- Significant renal insufficiency (S_{cr} > 3.0 mg/dL [>265 µmoL/L] or creatinine clearance <30 mL/min/1.73 m^2)
- Known significant liver impairment (baseline serum glutamic oxaloacetic transaminase [SGOT] or serum glutamic pyruvic transaminase [SGPT] and/or total bilirubin greater than three times the upper limit of normal)
- A previous history of tendinopathy associated with fluoroquinolones
- Pregnant, nursing or in whom pregnancy could not be excluded, or unreliable contraception used
- Known or suspected bacteremia or meningitis
- A 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; HIV testing not mandatory
- Been diagnosed with a rapidly fatal underlying disease (death expected within 6 months)
- Been previously enrolled in a trial with BAY 12-8039 (BAY 12-8039)
- Been taking an investigational drug in the last 30 days
- Patients known to have prolonged QTc intervals (inherited and sporadic syndromes of QTc prolongation)
- Patients receiving concomitant medication reported to increase the QTc interval, e.g., amiodarone, sotalol, disopyramide, quinidine, procainamide

MO Comment: The original protocol was amended on February 16, 1998 to lengthen the period of exclusion due to systemic antibiotics, from 24 hours to 7 days unless they were clinical failures on the previous antibiotic.

5. Randomization

Patients were randomized in a 1:1 ratio to BAY 12-8039 or cefuroxime axetil.

A single continuous stream randomization code was computer-generated by Bayer in blocks of 4. The investigator, the [redacted] or Bayer monitors, and the patients were blinded to the random codes.

6. Blinding

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 all dosing Days 1 to 10. 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.

All study medication was packaged in blister packs for each individual patient. Bayer and [redacted] monitors were to be notified immediately of any event requiring the code to be broken. The date and reason for breaking the code were to be recorded in the remote data entry (RDE) system.

MO Comment: The study was adequately blinded.

7. Study Procedures/ Observations

The following table from the NDA (Volume 228, page 45) was slightly modified by the MO:

Study Procedures

	Pre-Rx[A]	During-Rx (Day 3-5)	Post-Rx (Test of Cure) (7-14 days after last dose)	Post-Rx Follow-up Visit (27-31 days after last dose)
Informed consent	✓			
Evaluate patient eligibility	✓			
Medical history	✓			
Physical examination	✓			
Appropriate C&S (antral puncture)	✓B	✓B	✓B	
Gram stain/leukocyte count of aspirate	✓B	✓B	✓B	
Sinus x-ray (Waters' view)	✓	✓C	✓	✓C
Pregnancy test*	✓			
ECG**	✓	✓		
Serum sample for PK analysis		✓		
CBC/platelets/PT/PTT	✓	✓D	✓D	
Chemistries/UA/Theophylline***	✓	✓D	✓D	
Monitor clinical response		✓	✓	✓
Monitor adverse events		✓	✓E	✓E

A. Within 48 hours prior to onset of drug therapy.
B. At pre-therapy, if clinically indicated: thereafter, only in patients judged as clinical failures.
C. X-rays required during treatment only if treatment failure, and at 27-31 day follow-up visit only if relapse.
D. Tests that yield abnormal results considered potentially related to the study drug should be repeated at appropriate intervals to assess reversibility of the abnormalities.
E. Adverse events reported through 7 days post-therapy. Serious adverse events and deaths were reported through the 27-31 day follow-up period.

* Patients were enrolled based on a negative pregnancy test performed in the clinic. A serum pregnancy test was also sent to the laboratory.
** ECG was performed prior to study drug administration and during treatment.
*** SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, serum creatinine, blood urea nitrogen (BUN), uric acid, sodium, potassium, chloride, amylase, gamma GT, inorganic phosphorus, total protein, albumin, calcium, glucose, serum bicarbonate, cholesterol, and triglycerides. In all patients receiving theophylline, a pre-entry level was obtained and repeated at appropriate intervals throughout the study

MO Comment: As shown above, antral punctures and other microbiologic diagnostic tests were not routinely performed. The test of cure visit for this study (Day +7 to +14 post-therapy) is consistent with the recommendations in the draft DAIDP Evaluability Criteria guidance document and allows sufficient time off study drug to assess clinical response.

8. Evaluability Criteria

Efficacy Evaluability Criteria:

For a course of therapy to be judged valid for evaluating the efficacy of drug therapy, the following criteria must have been met and documented on the RDE system:

- acute sinusitis must have been confirmed at pre-treatment by the presence of signs and symptoms and positive radiography consistent with acute bacterial maxillary sinusitis;
- all inclusion/exclusion criteria must have been met;
- the study drug must have been given for a minimum of 72 hours if a treatment result was a failure;
- clinical evaluation must have been performed at the test of cure visit 7-14 days post treatment (an indeterminate designation at the test of cure invalidated the patient for efficacy evaluation);
- no other systemic antibacterial agent must have been administered with the study drug during the study period (up through Day 27-31 post-therapy evaluation) unless the patient was a treatment failure;
- adequate compliance must have been documented with ≥80% of oral study medication administered;
- no protocol violation occurred influencing treatment efficacy;
- the random code was not broken.

MO Comment: The evaluability criteria above are acceptable. The test of cure visit window was expanded from 7-14 days post-treatment to 7-21 days post-treatment in a protocol amendment dated February 16, 1998. According to the sponsor, this change was made prior to unblinding of the study results. The revised test of cure visit still allows sufficient time off study drug therapy to assess clinical response and to detect early relapse infections.

Safety Evaluability Criteria

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.

9. Statistical Analyses

Sample Size Determination

The protocol specified that 516 patients would be enrolled into the study. Based on the assumption of true failure rates of 10% for both treatment groups, the maximum allowable difference between treatments (delta) was 10%. Using these assumptions and alpha=0.025 (one-sided), the sponsor concluded that 206 valid patients per group would result in 80% power to test the null hypothesis of in-equivalence. With an assumed validity rate of 80%, approximately 258 patients per arm (516 total) would be required.

Efficacy

The primary population for analysis was specified as the subset of patients considered clinically evaluable. Intent-to-treat analyses were also planned for the demographic and efficacy variables.

Primary Efficacy Variable: Clinical response at the end of study drug therapy (7-14 day test of cure visit).

Secondary Efficacy variables: Clinical responses at the 3-5 Day during therapy visit and the 27-31 Day follow-up visit.

Clinical evaluation of study drug therapy:

During therapy (Day 3-5)

Improvement: clinically significant decrease in signs and symptoms of infection (study drug therapy was to be continued)

Failure: persistence of signs and symptoms of infection such that alternative antimicrobial therapy was required

Indeterminate: A clinical assessment was not possible to determine (e.g., early withdrawal ≤3 days of study drug treatment due to an adverse event.) Reasons for an indeterminate response must have been fully documented on the RDE system.

Test of cure (7-14 days after completion of study drug therapy)

After the completion of the therapy, the clinical response was graded as follows:

Resolution: No additional antimicrobial therapy was required. There was an improvement or absence of signs and symptoms related to the infection

Failure: No change, worsening or reappearance of the signs and symptoms of infection. Alternative antimicrobial therapy must have been provided.

Indeterminate: Patients in whom a clinical assessment was not possible to determine. Reasons for an indeterminate response must have been fully documented on the RDE system. Patients with an indeterminate response were invalid for efficacy evaluation.

MO Comment: The protocol does not define the degree of improvement or whether all signs and symptoms of the acute infection must be improved for designation of "resolution" at the test of cure visit. Patients with persistent sinus discomfort and purulent discharge could still be considered resolution even if their symptoms were only marginally improved using this classification. The "indeterminate" category is not clearly defined.

Follow-up (27-31 days after completion of therapy)

At the follow-up visit, clinical response was graded as follows for all patients who did not receive alternative anti-bacterial therapy prior to this visit:

Resolution: Clinically improved or resolved at the four week follow-up

Relapse: Clinically improved or resolved at the end of therapy, but reappearance of signs and symptoms of infection associated with acute sinusitis such that alternative therapy was required (patient did not return for further study evaluation)

MO Comment: One would reasonably expect all signs and symptoms of the acute infection to be completely resolved (rather than improved) by 27-31 days following completion of a full ten day course of effective study drug therapy.

Safety

Comparisons of the incidence rates of adverse events were tabulated in a descriptive manner by type (according to the COSTART glossary) and frequency, Tabulations were created for (1) all events and for (2) those events considered by the investigator to have a possible relationship to drug treatment.

Laboratory data were analyzed using descriptive statistics and identification of values outside the normal range.

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

See Appendix I for the list of patient enrollments by investigator/study site.

MO Comment: The study sites and investigators are acceptable. Enrolled patients were adequately distributed across study sites and geographical areas.

3. Demographics

The following table was compiled by the medical officer from Tables 14.1/4 and 14.1/11 in the NDA submission (Volume 228, pages 87, 95):

Demography, All-Treated Patients/Clinically Evaluable Patients
Study Number 100107

Characteristic	Moxifloxacin		Cefuroxime axetil		Total	
	ITT N =263	Eval N = 223	ITT N = 274	Eval N = 234	ITT N =537	Eval N = 457
Gender [N (%)]						
Male	99(38)	84(38)	107(39)	94(40)	206(38)	178(39)
Female	164(62)	139(62)	167(61)	140(60)	331(62)	279(61)
Race [N (%)]						
White	203(77)	176(79)	220(80)	186(79)	423(79)	362(79)
Black	22(8)	17(8)	21(8)	18(8)	43(8)	35(8)
Hispanic	22(8)	16(7)	19(7)	18(8)	41(8)	34(7)
Asian	16(6)	14(6)	10(4)	9(4)	26(5)	23(5)
Other	0	0	4(1)	3(1)	4(1)	3(1)
Age						
Mean	40	40	40	39		40
Median	39	39	39	39		39
Min. – Max.	18-76	18-76	18-78	18-78		18-78
Weight (kg)						
Mean	80	81	80	80		81
Median	77	77	79	79		78
Min. – Max.	42-151	42-150	46-147	48-147		42-150

NOTE: Max. = Maximum; Min. = Minimum.

MO Comment: Patient randomization for the study resulted in very comparable demographic characteristics for the two treatment arms for the all-treated patients population as shown above as well as for the clinically evaluable patients.

4. Reasons for Nonevaluability

As shown in the following table from the NDA (Volume 228, page 86), 267 and 275 patients were randomized to the moxifloxacin and cefuroxime axetil arms, respectively. Four patients in the BAY 12-8039 group and one patient in the cefuroxime axetil group who never returned after the initial office visit and reported no adverse events were excluded from the analysis of safety.

A total of 85 patients (44 in the moxifloxacin arm, 41 in the cefuroxime arm) were excluded from the clinically evaluable population. Lack of pre-therapy x-ray documentation within the specified time window was the most common inclusion/exclusion criteria violation. Other common reasons for exclusion were insufficient duration of therapy (< 80% of study drug received in patients who were

not treatment failures), no test of cure evaluation within the specified time window, and missing or invalid data from the primary efficacy evaluation.

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TABLE 14.1/3
PATIENT VALIDITY AND REASONS FOR EXCLUSIONS FROM ANALYSES

POPULATION: ALL RANDOMIZED PATIENTS

	BAY 12-8039 400MG	CEFUROXIME AXETIL	TOTAL
PATIENTS RANDOMIZED	267	275	542
VALID FOR SAFETY ANALYSIS	263 (99%)	274 (100%)	537 (99%)
IN PER-PROTOCOL EFFICACY ANALYSIS	223 (84%)	234 (85%)	457 (84%)
EXCLUDED FROM SAFETY ANALYSIS	4	1	5
LOST TO FOLLOW-UP	4	1	5
EXCLUDED FROM PER-PROTOCOL EFF ANALYSIS	44	41	85
INCLUSION/EXCLUSION CRITERIA VIOLATION	7	10	17
PRE-THERAPY X-RAY OUTSIDE WINDOW	4	6	10
NORMAL X-RAY	0	1	1
ELEVATED LABORATORY VALUES	2	1	3
< REQUIRED CLINICAL SYMPTOMS	1	1	2
PREVIOUSLY ENROLLED IN STUDY	0	1	1
NON-COMPLIANCE WITH STUDY DRUG	1	0	1
INSUFFICIENT DURATION OF THERAPY	14	10	24
VIOLATION OF TIME SCHEDULE	8	7	15
ESSENTIAL DATA MISSING OR INVALID	7	7	14
LOST TO FOLLOW-UP	4	1	5
USE OF PROHIBITED CONCOMITANT MEDICATION	3	5	8
USE OF PROHIBITED POST-TX MEDICATION	0	1	1

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MO Comment: The percentages of patients who were evaluable for the safety and efficacy analyses were generally high. The reasons for exclusion from the efficacy analysis do not appear to be biased by treatment arm. The medical officer's review of the datasets for patients with inclusion/exclusion criteria violations, radiographic documentation violations, insufficient duration of therapy, and test of cure window violations was consistent with the results presented in the table above.

As noted above, 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. Four of the six symptoms listed by the sponsor are also commonly seen with viral URI or inhalant allergic disease: nasal congestion, post-nasal drip, cough, and headache. As noted by Gwaltney[2], the clinical presentation of acute community-acquired bacterial sinusitis, in addition to these complaints, typically includes purulent nasal discharge, fever, and facial pain or erythema.

In order to lessen the likelihood of including patients with viral or allergic disease, the FDA evaluable population required at least one of the two 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. Review of the datasets revealed 15 patients whose baseline symptoms did not include either of these two signs/symptoms, and these patients were excluded from the FDA clinically evaluable population.

5. Prognostic Factors

The following table was compiled from the NDA tables (Volume 228, page 88) from the NDA and the medical officer's analysis of the past medical history data set. The table compares the two treatment arms with respect to factors of possible prognostic importance for the present infection:

PROGNOSTIC FACTORS
POPULATION: ALL PATIENTS VALID FOR EFFICACY

			BAY 12-8039 400MG (N=223)	CEFUROXIME AXETIL (N=234)	TOTAL (N=457)
HISTORY OF ALLERGIC RHINITIS		N(%)	56(25)	84(36)	140(31%)
HISTORY OF SINUSITIS		N(%)	12(5%)	11(5%)	23(5%)
SEVERITY OF INFECTION (P=0.033)	MILD	N (%)	11 (5)	4 (2)	15 (3)
	MODERATE	N (%)	165 (74)	194 (83)	359 (79)
	SEVERE	N (%)	47 (21)	36 (15)	83 (18)
BILATERAL EPISODES LAST 6 MOS (P=0.455)	MISSING	N (%)	4 (2)	2 (<1)	6 (1)
	0	N (%)	159 (71)	179 (76)	338 (74)
	1	N (%)	40 (18)	38 (16)	78 (17)
	2	N (%)	20 (9)	15 (6)	35 (8)
EPISODES (RIGHT) LAST 6 MOS (P=0.472)	MISSING	N (%)	4 (2)	2 (<1)	6 (1)
	0	N (%)	205 (92)	222 (95)	427 (93)
	1	N (%)	11 (5)	9 (4)	20 (4)
	2	N (%)	3 (1)	1 (<1)	4 (<1)
EPISODES (LEFT) LAST 6 MOS (P=0.050)	MISSING	N (%)	4 (2)	2 (<1)	6 (1)
	0	N (%)	205 (92)	227 (97)	432 (95)
	1	N (%)	11 (5)	5 (2)	16 (4)
	2	N (%)	3 (1)		3 (<1)

MO Comment: The percentage of patients with a history of allergic rhinitis is somewhat higher in the cefuroxime treatment arm, while the percentage of patients with severe infections (on enrollment into the study) was slightly higher in the moxifloxacin arm. Overall, the treatment arms were similar with respect to the above prognostic factors in both the clinically evaluable and safety (refer to NDA tables 14.1/12 and14.1/14) populations.

6. Pre-treatment Signs/Symptoms

The following table from the NDA (Volume 228, page 57) lists the baseline signs and symptoms rated as either moderate or severe for the clinically evaluable populations of the two treatment groups.

CLINICAL SIGNS AND SYMPTOMS AT STUDY ENTRY
POPULATION: PATIENTS VALID FOR EFFICACY

Severity of Pre-therapy Signs and Symptoms: Moderate and Severe Combined

	BAY 12-8039 (N = 223)	Cefuroxime (N = 234)
Frontal Headache	64%	61%
Malar Tenderness/Pain	55%	57%
Nasal Congestion	87%	86%
Post-Nasal Drainage/Discharge	74%	77%
Cough/Throat Clearing	66%	71%
Purulent Nasal Drainage	63%	72%

MO Comment: Physical findings of acute sinusitis were similarly distributed across treatment arms for the clinically evaluable patient populations as well as the safety population (refer to table 14.1/16 in the NDA submission). Overall, signs/symptoms were most commonly rated as being moderate in severity. As explained above, MO review of the datasets revealed that 15 patients reported neither purulent nasal drainage nor malar tenderness/pain, and these patients were excluded from the FDA evaluable population.

7. Reasons for Discontinuance

The following table from the NDA (Volume 228, page 53) outlines the reasons for patient withdrawal/discontinuation from the study:

Table I: Summary of Patient Disposition

	BAY 12-8039	Cefuroxime
Randomized	267	275
Completed study	239 (90%)	257 (93%)
Premature withdrawals/discontinuations (p = 0.100)[1]	28 (10%)	18 (7%)
Reason for withdrawal/discontinuation		
Adverse event (p = 0.038)[1]	15 (6%)	6 (2%)
Patient non-compliance	1 (<1%)	
Consent withdrawn	4 (1%)	3 (1%)
Insufficient therapeutic effect	2 (<1%)	1 (<1%)
Patient lost to follow-up	4 (1%)	4 (1%)
Protocol violation	2 (<1%)	4 (1%)

MO Comment: A higher percentage of moxifloxacin patients had adverse clinical events resulting in treatment discontinuation (see *Safety Review*). Otherwise the reasons for discontinuation appear reasonable and not biased by treatment arm. Review of the patients listed as discontinuing for "insufficient therapeutic effect" revealed that they had not received 3 days of study drug therapy and could not, therefore, be designated as treatment failures.

8. Radiological Findings

The following table was constructed from the medical officer's analysis of the radiographic datasets submitted by the sponsor.

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

Finding	Number (%) of Patients					
	Moxifloxacin		Cefuroxime		Total	
	ITT N=263	Eval N=223	ITT N=274	Eval N=234	ITT N=537	Eval N=457
Mucosal Thickening ≥ 6 mm	175(67)	143(64)	181(66)	152(64)	356(66)	295(65)
Opacification	132(50)	109(49)	127(46)	108(46)	259(48)	217(47)
Air/Fluid Level	65(25)	59(26)	79(29)	71(30)	144(27)	130(28)

MO Comment: The medical officer's review of the baseline radiographic data sets revealed only one patient not meeting entry criteria for the study. This patient (#128039) had, as a sole finding, less than 6 mm of mucosal thickening on [redacted] sinus x-ray. Accordingly, the sponsor designated this patient as invalid for the efficacy analysis.

9. Study Drug Exposure

The following table from the NDA (Volume 228, page 94) summarizes patient compliance with study drug therapy by treatment group based on pill counts during study visits.

COMPLIANCE WITH STUDY MEDICATION
POPULATION: ALL PATIENTS VALID FOR EFFICACY

	BAY 12-8039 400MG (N=223)	CEFUROXIME AXETIL (N=234)	TOTAL (N=457)
INTERVAL, N (%)			
<= 12 CAPSULES	3 (1%)	2 (<1%)	5 (1%)
>12 - 16 CAPSULES	1 (<1%)	0 (0%)	1 (<1%)
>16 - 18 CAPSULES	4 (2%)	1 (<1%)	5 (1%)
>18 - 19 CAPSULES	5 (2%)	3 (1%)	8 (2%)
>19 - 20 CAPSULES	210 (94%)	228 (97%)	438 (96%)
SUMMARY STATISTICS (CAPSULES)			
MEAN	20	20	20
SD	1	1	1
MINIMUM	8	7	7
MEDIAN	20	20	20
MAXIMUM	20	20	20

MO Comment: Compliance with study drug therapy in the clinically evaluable population was generally good with greater than 90% of patients receiving either 19 or 20 of 20 prescribed doses. Six patients received less than 80% of the prescribed doses. The medical officer confirmed that these patients were designated as early treatment failures.

10. 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 at the Test of Cure Visit (per Sponsor) Study 100107

Drug	Clinically Evaluable Patients		All-Treated Patients	
	Efficacy Rate	95% C.I.	Efficacy Rate	95% C.I.
Moxifloxacin	89.7% (200/223)	(-5.1%, 6.1%)	89% (210/235)	(-5.1%, 6.1%)
Cefuroxime	89.3% (209/234)		89% (219/246)	

MO Comment: The success rates were approximately 90% as anticipated by the sponsor. The confidence interval falls within the protocol-specified criteria for therapeutic equivalence (i.e., the lower bound of the confidence interval for the difference in response rates does not exceed 10%). Response rates were consistent across study centers (refer to NDA Table 14.2/2) and were consistent across demographic variables and prognostic factors (refer to NDA Table 14.2/4).

As previously described, the FDA evaluable population required at least one of the "cardinal" symptoms of acute sinusitis (i.e., malar pain/tenderness or purulent nasal discharge) during the pretreatment assessment. Consistent with the sponsor's definition of cure, these cardinal symptoms had to be resolved or improved at the test of cure visit to consider the patient a clinical cure. The FDA analysis in clinically evaluable patients (see table below) produced a lower efficacy rate for cefuroxime axetil and a more favorable confidence interval for the moxifloxacin treatment group compared to the sponsor's results. The medical officer agrees that the efficacy data at the test of cure visit support therapeutic equivalence of the two treatment arms.

Clinical Efficacy of Gatifloxacin and Moxifloxacin in Acute Sinusitis in Clinically Evaluable Patients (per MO) at Test of Cure Visit Study 100107

Drug	Clinically Evaluable Patients	
	Efficacy Rate	95% C.I.
Moxifloxacin	88.9% (193/217)	(-0.4%, 13.3%)
Cefuroxime	82.5% (188/228)	

Efficacy results at the followup visit (Day +27 to +31) are presented below as per the sponsor's and medical officer's analyses:

Clinical Efficacy of Gatifloxacin and Moxifloxacin in Acute Sinusitis in Clinically Evaluable Patients at Followup Visit Study 100107

Drug	Per Sponsor		Per Medical Officer	
	Efficacy Rate	95% C.I.	Efficacy Rate	95% C.I.
Moxifloxacin	90.5%(181/200)	(-9.4, 1.9)	77.4% (168/217)	(-12.1%, 3.8)
Cefuroxime	94.3%(197/209)		81.6% (186/228)	

MO Comment: The sponsor's analysis at the followup visit did not carry failures from the test of cure visit forward while the FDA analysis did. Thus, the FDA analysis in clinically evaluable patients produced a lower efficacy rate for both treatment arms. The response rate was slightly higher in the cefuroxime arm, and the confidence interval would fail to meet criteria for equivalence using the protocol-specified delta of 0.10 for the test of cure visit. However, given the lower efficacy rates in this conservative analysis, the FDA has previously applied an equivalence delta of 0.15 for efficacy rates when the highest efficacy rate fell between 80 and 90%. Using a 0.15 delta, equivalence would still be demonstrated.

11. Safety

Deaths

No patients died during the study.

Serious Adverse Events

Only one serious adverse event was reported: Patient 17001, in the BAY 12-8039 group reported chest pain 11 days after the end of study-drug therapy. The event was considered not drug related by the investigator. The patient was hospitalized for observation and treatment and an electrocardiogram taken on admission proved normal.

All Adverse Events

As shown in the table below from the NDA submission (Volume 228, page 64) a slightly higher percentage of patients receiving BAY 12-8039 reported adverse events compared to patients receiving cefuroxime. The most common adverse events in both treatment arms involved the digestive system, body as a whole, nervous system, and respiratory system. Of these, only respiratory adverse events were more common in the cefuroxime arm.

Number and Percent of Patients with Adverse Events by Body System

Body System	BAY 12-8039 (N=263)	Cefuroxime (N=274)
Any body system	126 (48%)	112 (41%)
Body as a whole	49 (19%)	36 (13%)
Cardiovascular	8 (3%)	5 (2%)
Digestive	65 (25%)	39 (14%)
Metabolic & nutritional	4 (2%)	0 (0%)
Musculoskeletal	3 (1%)	4 (1%)
Nervous	39 (15%)	20 (7%)
Respiratory	14 (5%)	34 (12%)
Skin and appendages	14 (5%)	12 (4%)
Special senses	4 (2%)	11 (4%)
Urogenital	5 (2%)	12 (4%)

Excerpted from Table 14.3.1/2.

The following table from the NDA submission (Volume 228, page 67) summarizes the specific drug-related adverse events by treatment arm (which were experienced by at least 2% of patients in either arm).

Number and Percent of Patients with Drug-Related Adverse Events Occurring in at Least 2% of Either Treatment Group

Body System	BAY 12-8039 (N=263)	Cefuroxime (N=274)
Any event	96 (37%)	70 (26%)
Headache	12 (5%)	8 (3%)
Abdominal pain	5 (2%)	3 (1%)
Asthenia	5 (2%)	4 (1%)
Nausea	28 (11%)	11 (4%)
Diarrhea	18 (7%)	17 (6%)
Vomiting	9 (3%)	3 (1%)
Dry mouth	5 (2%)	3 (1%)
Dyspepsia	5 (2%)	5 (2%)
Dizziness	13 (5%)	7 (3%)
Nervousness	7 (3%)	2 (<1%)
Insomnia	4 (2%)	3 (1%)
Sweating	5 (2%)	1 (<1%)

MO Comment: The medical officer's analysis of the adverse events considered to be drug-related produced very similar results to the sponsor's table above. Gastrointestinal complaints, especially nausea, diarrhea and vomiting, were the most common events in each group and were more frequently seen in the moxifloxacin treatment arm. Fifteen moxifloxacin patients (6%) and 6 cefuroxime patients (2%) discontinued therapy due to adverse events. Discontinuations were most commonly due

to gastrointestinal or nervous systems events in moxifloxacin patients and hives/pruritis/allergic reactions in cefuroxime treated patients.

The following adverse clinical events associated with other drugs in the fluoroquinolone class were not commonly seen with moxifloxacin therapy during this study:

Heptotoxicity:

Only one patient with abnormal liver function tests from the pretreatment evaluation discontinued the study due to further slight increases in serum GGT (113–>154), SGPT(135–>162), and LDH (264→292). All values had already begun normalizing at the time of study drug discontinuation.

Central Nervous System:

No cases of seizures, convulsions, or psychosis were reported during therapy. Dizziness was more common in the moxifloxacin group (5%) than in the cefuroxime group (3%). CNS excitation (nervousness, insomnia) was somewhat more frequently reported with moxifloxacin treatment compared to cefuroxime treatment (3 of these patients discontinued treatment in the moxifloxacin arm).

Tendonopathy:

No cases of rupture of the shoulder, hand or Achilles tendon were reported.

Rash

- **Drug-related rashes were noted in 2 patients in each treatment arm.**

Anaphylaxis

One drug-related allergic reactions was noted in a moxifloxacin-treated (compared to one cefuroxime-treated patient):

Patient 27-27031: A 38 year old female with a history of seasonal allergies who developed moderate "buccal itching lips" and moderate swelling of the nostrils after two doses of study drug. She was successfully managed with Claritin and discontinued study medication.

Cardiac Effects

Patient 8-8073 discontinued moxifloxacin due to QT_c prolongation. Refer to Integrated Summary of Safety (Dr. Leonard Sacks) for a comprehensive review of this issue.

Clinical Laboratories

The following table from the NDA (Volume 228, page 69) shows lab abnormalities occurring in at least 5% of subjects (either treatment group):

Table II. Number and Percent of Patients with Laboratory Abnormalities Occurring in at Least 5% of Either Treatment Group

Laboratory Variable	BAY 12-8039 (N=263)	Cefuroxime (N=274)
High		
Lymphocytes	12/242 (5%)	8/263 (3%)
Eosinophils	31/227 (14%)	31/242 (13%)
PT	54/202 (27%)	34/215 (16%)
Serum glucose	33/227 (15%)	45/236 (19%)
Phosphorus, inorg	11/247 (4%)	16/259 (6%)
Chloride	32/241 (13%)	21/255 (8%)
SGPT/ALT	4/235 (2%)	12/254 (5%)
Cholesterol, total	32/147 (22%)	28/168 (17%)
Triglycerides	34/192 (18%)	33/215 (15%)
Low		
Hematocrit	29/220 (13%)	29/240 (12%)
Hemoglobin	27/220 (12%)	23/244 (9%)
Neut (segs) absolute ct	11/243 (5%)	6/261 (2%)
APTT	11/223 (5%)	19/249 (8%)
Serum glucose	19/244 (8%)	12/257 (5%)
Uric acid	14/212 (7%)	20/228 (9%)
Urine		
Appearance, urine	38/188 (20%)	54/208 (26%)
Protein, urine	13/221 (6%)	13/243 (5%)
Blood, urine	27/214 (13%)	25/228 (11%)
RBC, urine sediment	23/222 (10%)	22/241 (9%)

MO Comment: Elevation of prothrombin time, cholesterol, and chloride occurred more frequently in the moxifloxacin treatment arm. Elevation of liver function tests (SGPT/ALT) and glucose occurred more frequently in cefuroxime treated patients. As described above, only one patient (in the moxifloxacin treatment arm) discontinued the study due to modest elevation of pre-existing abnormal liver function test results.

C. Medical Officers Summary/Conclusions

This prospective, randomized study compared the safety and efficacy of moxifloxacin 400 mg po qd to cefuroxime 250 mg po bid for 10 days in patients with acute sinusitis. The design and conduct of the study were generally acceptable. According to the sponsor, the clinical efficacy rates at the test of cure visit (Day +7 to +21 post-therapy) were 89.7% and 89.3% for the clinically evaluable moxifloxacin and cefuroxime treatment arms, respectively; 95% C.I. =(-5.1%, 6.1%). For the all-treated patients population, the sponsor's response rates were 89% in both treatment arms; 95% C.I. (-5.1%, 6.1%). These results meet the protocol-defined criteria for clinical equivalence (delta = 0.10).

The medical reviewer was concerned that the inclusion criteria in the protocol could allow inclusion of patients with allergic rhinitis or viral upper respiratory tract infection. Therefore, the FDA clinically evaluable 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 88.9% and 82.5%, respectively; 95% C.I. = (0.4%, 13.3%). Again, protocol-defined criteria for equivalence are clearly met.

Drug-related adverse events occurred more commonly in the moxifloxacin group (37%) compared to the control group (26%), and were mainly related to the gastrointestinal (nausea, vomiting, diarrhea) and the nervous system (insomnia, nervousness, dizziness). The incidence of laboratory abnormalities was similar between the two treatment arms. However, elevation of the prothrombin time, cholesterol and chloride occurred more frequently in the moxifloxacin treatment arm. Elevation of liver function tests (SGPT/ALT) and glucose occurred more frequently in cefuroxime treated patients.

The medical officer concludes that the efficacy data from this study support the approval of moxifloxacin for the acute sinusitis indication. The safety profile of moxifloxacin in this study was acceptable (review of ECG data to be done per Dr. Leonard Sacks).

APPEARS THIS WAY
ON ORIGINAL