

- III. Study No. BAY 12-8039/0161: "Prospective, randomised, double-blind, multi-centre, multi-national clinical trial comparing the safety and efficacy of MOXIFLOXACIN (BAY 12-8039), 400 mg q.d. with cefuroxime-axetil, 250 mg b.i.d. in the treatment of patients with acute sinusitis"

A. Overview

1. Objectives:

The objectives of this study were to compare the safety and efficacy of oral BAY 12-8039 administered orally at 400 mg q.d. for 10 days versus cefuroxime-axetil 250 mg b.i.d. for 10 days in the treatment of adult patients with clinically suspected acute bacterial sinusitis.

MO Comment: See comments regarding use of cefuroxime axetil as a comparator agent for acute sinusitis trials above in the *Objectives* section for Study 100107 above. The dosage, frequency and duration of cefuroxime therapy are consistent with the approved labeling for this indication.

2. Design

This was a prospective, randomized, multi-center, double-blind Phase III study conducted at 47 sites across Europe to compare the efficacy and safety of BAY 12-8039, 400 mg p.o. q.d., for ten days with that of cefuroxime-axetil, 250 mg p.o. b.i.d. for 10 days, in the treatment of outpatients with clinically suspected acute bacterial sinusitis

3. Inclusion Criteria – see Study 100107

MO Comment: The inclusion criteria are identical to Study 100107 with one exception: patients were not required to have symptoms for at least 7 days duration in the present study. Please refer to MO Comments in Study 100107 above regarding inclusion criteria.

4. Exclusion Criteria

- Age below 18 years.
- A history of hypersensitivity to either of the study drugs or related compounds.
- Severe cardiac failure (class IV of the NYHA classification).
- Having received a systemic antibacterial agent within 48 hours of enrolment, unless the patient was a clear clinical failure.
- Known renal insufficiency (serum creatinine > 265 µmol/l).
- Requirement for any concomitant systemic antibacterial agent.
- Previous sinus surgery (antral sinus puncture not considered as surgery).

- A history of chronic sinusitis with more than four weeks of continuous symptoms.
- Recurrence of more than two documented episodes of acute sinusitis within the previous six months.
- For female patients: pregnancy, lactation or use of inadequate contraception. (Note: Female patients of child-bearing potential must give a negative serum pregnancy test – negative urine test before enrolment to be confirmed by serum test – unless they had been surgically sterilised).
- Neutropenia (neutrophil count < 1000/mm³) due to malignancy or chemotherapy.
- Known liver disease or significant liver impairment (ALT/AST and/or baseline bilirubin above three times upper normal limit).
- Patients known to have congenital or sporadic syndromes of QTc prolongation, or are receiving concomitant medication reported to increase the QTc interval, e.g. amiodarone, sotalol, disopyramide, quinidine, procainamide, [REDACTED]
- Known or suspected bacteraemia or meningitis, including infiltrated neighbouring tissue of the sinus.
- Known AIDS (guideline, where available, CD4 count below 200/mm³).
- Severe infection requiring parenteral antimicrobial therapy or mechanical ventilatory support.
- Previous history of tendinopathy with fluoroquinolones.
- Participation in a clinical trial within the previous three months.
- Previous enrolment in this study.

MO Comment: The exclusion criteria are acceptable.

5. Randomization/Blinding

A computer-generated randomization list was prepared in advance at Bayer for the blister packs supplied to each study center. All patients received identical film-coated capsules b.i.d. for ten days. During this double-blind study, the randomization code for a patient could be broken in the case of a medical emergency, e.g. overdose, at the request of the investigator, the Drug Surveillance Unit, or the Medical Director. Breaking the code had to be followed by full documentation, and the study monitor was to be informed within 24 hours. Breaking of the random code resulted in invalidity of the patient for efficacy evaluation.

MO Comment: The study was adequately randomized and blinded.

6. Study Procedures/ Assessments

The table below from the NDA submission (Volume 237, page 48) summarizes the study visits and procedures. Patients meeting inclusion/exclusion criteria were enrolled and material for cultures was obtained by [redacted]

[redacted] antral puncture (only in a small number of patients). Patients were seen once during dosing (Days 7-9) or earlier if they failed to respond to therapy. A test of cure evaluation was performed 4-7 days after the end of therapy to assess clinical and bacteriological response. Patients were also seen at a followup visit 27-31 days following the end of treatment for clinical evaluation and assessment of adverse events.

Study flow chart (adapted from Appendix 12.1 of the study protocol)

Procedure ↓	Activity → When performed →	Screening	Dosing	One visit during dosing	One visit after dosing	One follow-up visit
		See note 1	Days 1-10	Days 7-9	Test-of-cure Day (14-17)	Days 37-41
Recording of medical history		+				
Assessment of patient eligibility		+				
Physical examination		+		+		
Signed informed consent		+				
Vital signs		+		+		
Microbiological culture and susceptibility test (puncture, cannulation or swab)		+			+	+ 2
Occipitontental radiography		+			+ 3	
Haematology		+		+ 4		
Blood chemistry/urinalysis		+		+ 4		
Clinical evaluation/Clinical signs		+5		+	+	+
Monitoring of adverse events		-		+	+	
Drug intake (out-patient basis)			+ 6			

- 1 Screening was to take place no more than 48 hours before commencement of dosing on day 1
- 2 Recommended in case of relapse
- 3 Optional
- 4 Tests that yielded abnormal results considered potentially related to the study drug were to be repeated at appropriate intervals during follow-up to assess reversibility of the abnormalities
- 5 Clinical signs only
- 6 Either BAY 12-8039 on days 1-10 or cefuroxime-axetil on days 1-10. For details, see Table 2 above

MO Comments: The medical reviewer notes several problems with the study design:

- [REDACTED] According to the IDSA guidelines and the draft ODE IV evaluability criteria guidance document for acute sinusitis, antral puncture of the maxillary sinus is the only currently acceptable procedure for bacteriological documentation of infection. While early reports suggest the potential value of endoscopically-guided cultures of the middle meatus in identifying the microbial etiology for the three major pathogens in acute maxillary sinusitis^{3,4}, further studies are required to define the role of this procedure in clinical trials. In particular, interpretation of endoscopically-guided cultures may be complicated by contamination with nasal cavity flora (particularly staphylococcal species)^{5,6}.
- The test of cure evaluation time window (4-7 days post-therapy) does not allow sufficient time off study drug to assess efficacy. The draft ODE IV evaluability criteria guidance document recommends that the test of cure visit occur approximately 1-2 weeks following completion of therapy. For the FDA analysis of efficacy, the medical officer will therefore consider the followup visit (27-31 days post-therapy) as the test of cure visit.
- The protocol requires only a screening radiological examination; the post-therapy radiological examination is optional. The draft ODE IV evaluability criteria guidance document recommends a followup radiological study (preferably the same modality used during the screening visit) at the test of cure visit. Patients should have no worsening of the post-therapy exam compared to the screening exam to be considered a "cure."

7. Evaluability Criteria

Intent-to-treat (ITT) population: All patients receiving any dose of study drug had been randomized, since the drug was dispensed in pre-randomized blister packs. Thus the ITT population (defined in the study protocol as those patients who had been randomized and had received at least one dose of study drug) and the safety population (all patients who had received at least one dose of study drug) were identical in this study.

Per protocol (PP) population: For a patient to be judged valid for evaluation of the efficacy of therapy, the following criteria had to be met and documented:

- Acute sinusitis confirmed before treatment by signs and symptoms and positive radiographic results.
- Study drug given for ≥ 3 full days (in cases of failure) or $>80\%$ compliance (in cases of resolution).
- No other systemic antimicrobial agent administered concomitantly, unless the patient was a treatment failure.
- Documented compliance $\geq 80\%$.
- No protocol violations considered likely to influence the efficacy of treatment.
- Randomization code not broken prematurely.
- No essential data (i.e., primary efficacy variable) missing or indeterminate.

For microbiological assessment, the following criterion was also applied:

- At least one causative organism identified in an appropriate (i.e., taken according to the three protocol-specified methods: [REDACTED])

pre-therapy culture, and an appropriate post-therapy bacteriological evaluation (positive or negative culture or 'no material to culture') available



8. Statistical Analyses

Sample Size Determination

The sample-size calculation assumed: a failure rate of 15 % in the control group, an equivalence (clinically relevant) δ of 15%, $\alpha= 2.5\%$ (one-sided) and $\beta= 20\%$ (obtained at a failure rate of 15 % in the cefuroxime-axetil group). On this basis, the sample size estimate was 126 valid patients per treatment group, including 15% to take account of the multicenter design of the study (sample size formula from Rodary *et al.*, reference 16 in the NDA study report). With an assumed validity rate of about 80%, 158 patients were to be recruited in each treatment group, implying a total of at least 316 patients recruited.

MO Comment: The assumptions (rates of failure and clinical evaluability) made in this calculation are reasonable.

Efficacy

Primary Efficacy Variable: Clinical response in the per-protocol population at the test of cure visit (day 4-7 post-therapy) .

Secondary Efficacy Variables: Clinical response at the during therapy (days 7-9) and followup visits (days 27-31) and the bacteriological response at the end of therapy.

Refer to review of Protocol 100107 for definitions of clinical response.

Safety

Safety analyses were identical to protocol 100107 above.

B. Study Results

A total of 497 patients were enrolled in the trial: 246 patients in the moxifloxacin arm and 251 patients in the cefuroxime arm. According to the sponsor's analysis, 217 (88%) moxifloxacin-treated patients and 222 (88%) cefuroxime-treated patients were evaluable for the per protocol analysis. Patients were enrolled from 47 centers

in seven countries. See Appendix II for a listing of enrollment by study center and treatment arm.

MO Comment: As shown in Appendix II, the percentage of enrolled subjects who were considered evaluable for the per protocol analysis was high and generally consistent across treatment centers.

1. Demographics

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

**Demography, Per Protocol Population
 Study 0161**

Characteristic	Moxifloxacin N = 217	Cefuroxime-axetil N = 222
<u>Gender</u> [N (%)]		
Male	107 (49.3)	98 (44.1)
Female	110 (50.7)	124 (55.9)
<u>Race</u> [N (%)]		
Caucasian	166 (76.5)	165 (74.3)
Not Reported	51 (23.5)	57 (25.7)
<u>Age</u>		
Mean	40.5	42.3
Median	39	40
Min. - Max.	20-72	18-72
<u>Weight</u> (kg)		
Mean	72.8	72.7
Median	71	70
Min. - Max.	50-115	45-138

MO Comment: Patient randomization for the study resulted in very comparable demographic characteristics for the two treatment arms of the per protocol population. The population was homogenous with respect to race (all Caucasian). Race was not reported for patients at French study sites due to legal reasons.

2. Reasons for Nonevaluability

As shown in the following table from the NDA (Volume 237, page 73), 29 patients in each arm were excluded from the per protocol population. The most common reasons were use of prohibited medications and violations of the time schedule or inclusion/ exclusion criteria.

Reason for exclusion from efficacy analysis, PP population

(all patients enrolled)

	BAY 12-8039 n = 246		Cefuroxime-axetil n = 251	
Any reason	29	(11.8%)	29	(11.6%)
Violation of inclusion/ exclusion criteria	8	(3.3%)	11	(4.4%)
Non-compliance with study drug	3	(1.2%)	1	(0.4%)
Insufficient duration of therapy	6	(2.4%)	6	(2.4%)
Violation of time schedule	14	(5.7%)	15	(6.0%)
Informed consent withdrawn	3	(1.2%)	1	(0.4%)
Essential data missing or invalid	8	(3.3%)	9	(3.6%)
Use of prohibited concomitant medication	14	(5.7%)	6	(2.4%)
No study medication	1	(0.4 %)	0	(0 %)

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

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

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3. Description of Current Infection/Prognostic Factors

The following table was obtained from the NDA (Volume 237, page 286):

3. Description of Current Infection/Prognostic Factors

The following table was obtained from the NDA (Volume 237, page 286):

TABLE 14.1.2/1.2 PP: DESCRIPTION OF ACUTE SINUSITIS
POPULATION: ALL PATIENTS VALID PER PROTOCOL
REGION: ALL REGIONS

		TREATMENT GROUP						P-VALUE OF CHECK OF HOMOGENEITY
		DAY 12: 8339 (N=319)		CERIVIRINE - AERTEL (N=222)		ALL TREATMENT GROUPS COMBINED (N=541)		
		#	%	#	%	#	%	
DAYS OF PRESENT INFECTION (PATIENT THERAPY)	0 - 4 DAYS	81	27.3	76	34.2	157	28.8	
	4 - 6 DAYS	60	27.6	47	21.2	107	24.6	
	≥ 7 DAYS	76	35.0	99	44.6	175	39.9	
LOCATION OF PRESENT INFECTION: MULTIPLE SITES POSSIBLE	FRONTAL	45	20.7	33	14.9	78	17.8	
	MAXILLARY LEFT	43	19.8	49	22.1	92	21.0	
	MAXILLARY RIGHT	54	24.8	42	18.9	96	21.9	
	MAXILLARY BILATERAL	112	51.1	120	58.1	242	55.1	
	ETHMOID LEFT	9	4.1	5	2.3	14	3.2	
	ETHMOID RIGHT	5	2.2	3	1.4	7	1.8	
	ETHMOID BILATERAL	15	6.9	15	6.8	30	6.8	
NUMBER OF INVOLVED SITES	≤ 2	179	82.5	188	84.7	367	83.6	0.5962
	≥ 3	38	17.5	34	15.3	72	16.4	
SEVERITY OF PRESENT INFECTION	MILD	14	6.5	15	6.8	29	6.6	0.8280
	MODERATE	132	60.8	140	63.1	272	62.0	
	SEVERE	71	32.7	67	30.2	138	31.4	
NO. OF EPISODES IN THE LAST 6 MONTHS	0	182	83.9	181	81.5	363	82.7	
	1	33	15.2	36	16.2	69	15.7	
	2	2	0.9	5	2.3	7	1.6	
	≥ 3							

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

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4. Pretreatment Signs/Symptoms

The following table was obtained from the NDA (Volume 237, page 330):

NDA # 21-061
Acute Sinusitis Indication

4. Pretreatment Signs/Symptoms

The following table was obtained from the NDA (Volume 237, page 330):
CLINICAL SIGNS AND SYMPTOMS AT STUDY ENTRY (PER PROTOCOL)

		DAY 12-13 (N=333)		DEFERRED TREATMENT-ALTERNATIVE (N=322)		ALL TREATMENT GROUPS COMBINED (N=655)		P-VALUE OF TEST OF HOMOGENEITY
		#	%	#	%	#	%	
SINUSITIS	MODERATE	1	0.3			1	0.2	
	NOT REPORTED	214	99.7	222	100.0	438	99.8	
FRONTAL HEADACHE	NONE	39	18.0	44	21.6	87	19.8	0.4901
	MILD	55	25.3	57	29.7	112	25.5	
	MODERATE	72	33.2	73	32.9	145	33.0	
	SEVERE	31	23.5	44	19.4	95	21.6	
NASAL TENDRINESS/PAIR	NONE	40	22.3	53	27.9	141	23.0	0.2949
	MILD	60	27.4	47	23.2	107	24.4	
	MODERATE	73	33.6	93	41.0	166	37.4	
	SEVERE	24	18.4	31	16.0	67	15.7	
NASAL CONGESTION	NONE	7	3.2	4	1.8	11	2.5	0.5017
	MILD	42	19.4	34	16.2	78	17.8	
	MODERATE	115	53.0	132	59.3	247	56.3	
	SEVERE	53	24.4	50	23.5	103	23.5	
SOFT-NASAL DRAINAGE / D. SWARMS	NONE	31	14.3	27	12.3	58	13.2	0.3205
	MILD	60	27.4	47	21.2	107	24.4	
	MODERATE	83	42.8	122	50.3	205	46.7	
	SEVERE	22	18.2	24	16.2	49	15.7	
CATCH/THROAT CLEARING	NONE	81	38.2	97	43.7	180	41.0	0.2531
	MILD	44	21.2	44	19.8	90	20.5	
	MODERATE	44	29.5	67	30.2	111	29.9	
	SEVERE	24	11.1	14	6.3	38	8.7	
PURULENT NASAL DRAINAGE	NONE	19	7.5	15	7.0	34	7.7	0.7808
	MILD	14	5.5	8	3.7	22	5.2	
	MODERATE	99	45.6	91	42.3	190	48.0	
	SEVERE	32	18.4	28	16.7	60	18.0	

MO Comment: The treatment groups were well balanced with respect to baseline symptoms by severity.

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5. Reasons for Discontinuations

The following table was obtained from the NDA (Volume 237, page 71):

Reasons for discontinuations (all patients enrolled).

	BAY 12-8039 n = 246 ¹		Cefuroxime-axetil n = 251		All patients n = 497 ¹	
	n	%	n	%	N	%
Any reason	14 ¹	5.7	15	6.0	29 ¹	5.8
Adverse event	3	1.2	6	2.4	9	1.8
Consent withdrawn	4	1.6	1	0.4	5	1.0
Insufficient efficacy	3	1.2	1	0.4	4	0.8
Lost to follow-up	1 ¹	0.4	1	0.4	2 ¹	0.4
Protocol violation	4	1.6	5	2.0	9	1.8
Cured	0	0.0	1	0.4	1	0.2

1) including patient no. 39001 (who did not receive study medication)

Note that for any given patient, more than one reason may apply.

MO Comment: Patients designated as "insufficient efficacy" received less than the required three days of therapy and thus could not be designated treatment failures. Discontinuation due to adverse events was uncommon in both arms.

6. Radiographic Findings

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

**Pre-treatment Radiographic Data for Maxillary Sinuses
Protocol 0161
Safety and Efficacy Populations**

Finding	Number (%) of Patients					
	Moxifloxacin		Cefuroxime		Total	
	ITT N=246	Eval N=217	ITT N=251	Eval N=222	ITT N=497	Eval N=439
Mucosal Thickening \geq 6 mm	167(68)	148(68)	168(67)	158(71)	335(67)	306(69)
Opacification	150(61)	143(66)	142(57)	131(59)	292(59)	274(63)
Air/Fluid Level	46(19)	39(18)	63(25)	55(25)	109(22)	94(21)

MO Comment: The treatment arms were similar in pathological findings consistent with acute sinusitis. The medical officer verified that eleven patients failing to meet radiographic inclusion criteria and were excluded from the per protocol population.

7.- Study Drug Exposure

Refer to NDA Table 14.1.3/2 for complete details of study drug usage. Compliance with both treatment regimens was good: 97.2% of moxifloxacin-treated patients and 98.6% of cefuroxime-treated patients in the per protocol population received between 18 and 21 doses of study medication.

8. Efficacy

Clinical Efficacy

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

**Clinical Efficacy of Moxifloxacin and Cefuroxime in Acute Sinusitis
 at the Test of Cure Visit (per Sponsor)
 Study 0161**

Drug	Per Protocol Patients		All-Treated Patients	
	Efficacy Rate	95% C.I.	Efficacy Rate	95% C.I.
Moxifloxacin	93.5% (203/217)	(-5.5, 3.4)	90.6% (222/245)	(-5.2, 4.8)
Cefuroxime	94.6% (210/222)		90.8% (228/251)	

MO Comments: Efficacy rates at the sponsor's test of cure visit (Day +4 to +7 post-therapy) were high in both treatment arms, and the 95% confidence intervals meet the protocol-specified criteria for clinical equivalence to cefuroxime in both the per protocol and all-treated patients populations. The success rates were consistent across countries and were all greater than 90% in the per protocol population (refer to NDA Table 14.2.1 PP).

As previously described, the FDA evaluable population had to have at least one of the cardinal symptoms of acute sinusitis at baseline (i.e., malar pain/tenderness or purulent nasal discharge). Consistent with the sponsor's definition of cure, these symptoms had to be resolved or improved at the test of cure visit to consider the patient a clinical cure. To allow adequate time off therapy to assess treatment response the FDA analysis used the followup visit (Day +27 to +31 post-therapy as the test of cure visit. As shown in the table below, the response rates for both treatment arms are lower compared to the sponsor's analysis. However, the confidence interval still meets the protocol-defined criteria for equivalence. The medical officer agrees that the efficacy data (by both FDA and sponsor's analysis) support clinical equivalence of the two treatment arms.

**Clinical Efficacy of Cefuroxime and Moxifloxacin in Acute Sinusitis
in Clinically-Evaluable Patients (per MO) at Test of Cure Visit
Study 0161**

Drug	Per Protocol Patients	
	Efficacy Rate	95% C.I.
Moxifloxacin	87.1% (183/210)	(-8.3%, 5.0%)
Cefuroxime	88.8% (190/214)	

Bacteriological Efficacy

Only 9 moxifloxacin-treated patients had bacteriological documentation of infection by antral puncture. The large majority of patients underwent "middle meatus cannulation" or "meatal swab," and neither of these techniques is currently acceptable to the FDA for documentation of microbial etiology. As shown in the NDA table below (Volume 237, page 95), bacteriological success rates were high in both treatment arms:

Bacteriological responses by patient at the test-of-cure (TOC) visit

Bacteriological response	BAY 12-8039		Cefuroxime-axetil	
	(n = 86)		(n = 72)	
	n	%	N	%
Bacteriological success rate	84	97.7	68	94.4
Eradication	49	57.0	40	55.6
Presumed eradication	35	40.7	28	38.9
Bacteriological failure rate	2	2.3	4	5.6
Eradication with superinfection	0	0	1	1.4
Persistence (1)	1	1.2	3	4.2
Presumed persistence	1	1.2	0	0

1) Including persistence with superinfection

Eradication or Presumed Eradication Rates for moxifloxacin-treated patients for the three major sinusitis pathogens in the microbiologically evaluable population were as follows:

Organism	Eradication/Presumed Eradication [N/Total Number of Organisms (%)]
<i>Streptococcus pneumoniae</i>	36/38 (94.7)
<i>Haemophilus influenzae</i>	17/17 (100)
<i>Moraxella catarrhalis</i>	10/10 (100)

MO Comment: The methodology for obtaining culture specimens is unacceptable to the FDA for documenting microbiological efficacy of moxifloxacin. Study D94-023 used antral taps for documentation and was designed to demonstrate the activity of moxifloxacin against the three major pathogens above for the NDA.

10. Safety

Deaths

No deaths were reported in this study.

Serious Adverse Events

Six serious events occurred during the study, 5 in the moxifloxacin group and 1 in the cefuroxime axetil group. None were considered related to study drug therapy.

All serious adverse events

Treatment group	Day started	Patient no.	Relationship to study drug	COSTART term (investigator's term)	Outcome
BAY 12-8039	+26	6004	none	Tachycardia (Tachyarrhythmia)	Resolved
	+9	48008	none	Sinusitis (Sinusitis)	Resolved
	+32			Surgery (Conchotomy, surgery of the septum, infundibulotomy, ethmoidectomy)	
	+21	9004	none	Diagnostic procedure (Microlaryngoscopy)	Resolved
	+7	36005	none	Sinusitis (Sinusitis worsening)	Resolved
Cefuroxime-axetil	+1	13005	none	Tenosynovitis (Syndrome of the carpal tunnel)	Improved

MO Comment: Patient 6004 was a diabetic patient with a history of alcoholism and a primary cardiomyopathy. The onset of his tachyarrhythmia over three weeks after completion of therapy is thus more likely due to his underlying medical problems than to the study drug. Patients 48008 and 36005 were treatment failures who ultimately required surgical drainage of their sinuses.

All Adverse Events

The following table from the NDA (Volume 237, page 114) shows adverse events with an incidence of at least 2% in either treatment arm without respect to causality:

Adverse events (ITT population) recorded in at least 2% of either treatment group

Body system (any event)	Most frequent AEs	BAY 12-8039		Cefuroxime- axetil		All patients	
		n = 245		n = 251		n = 496	
		n	%	n	%	n	%
Any system	Any AE	81	33.1	73	29.1	154	31.0
Body as a whole		25	10.2	15	6.0	40	8.1
	Abdominal pain	10	4.1	5	2.0	15	3.0
	Asthenia	7	2.9	6	2.4	13	2.6
Digestive system		49	20.0	39	15.5	88	17.7
	Diarrhea	24	9.8	16	6.4	40	8.1
	Liver function tests abnormal	9	3.7	7	2.8	16	3.2
	Nausea	12	4.9	9	3.6	21	4.2
Nervous system		15	6.1	11	4.4	26	5.2
	Dizziness	5	2.0	2	0.8	7	1.4
	Vertigo	3	1.2	6	2.4	9	1.8
Respiratory system		10	4.1	12	4.8	22	4.4
	Rhinitis	0	0	6	2.4	6	1.2

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

The following table from the study report (Volume 237, page 115) shows drug-related adverse events of at least 2% incidence for either treatment arm:

Acute Sinusitis Indication

Adverse events rated as at least remotely drug-related (ITT population),
recorded in at least 2 % in either treatment group

Body system (any event)	Most frequent AEs	BAY 12-8039		Cefuroxime- axetil		All patients	
		n	%	n	%	n	%
Any system	Any AE	65	26.5	55	21.9	120	24.2
Body as a whole		21	8.6	11	4.4	32	6.5
Digestive system	Abdominal pain	10	4.1	5	2.0	15	3.0
	Asthenia	6	2.4	5	2.0	11	2.2
	Diarrhea	21	8.6	14	5.6	35	7.1
	Liver function test abnormal	6	2.4	7	2.8	13	2.6
	Nausea	11	4.5	9	3.6	20	4.0

MO Comment: The overall rate of drug-related adverse events were slightly higher for the moxifloxacin arm compared to the cefuroxime arm (except for liver function test abnormalities). Only three patients in the moxifloxacin arm discontinued therapy due to adverse event compared to six patients in the cefuroxime arm. A brief description of the three moxifloxacin patient discontinuations due to adverse events is shown below:

Treatment group	Day started	Patient no.	COSTART term (investigator's term)
Moxifloxacin	Day 6	11012	Vertigo (Vertigo subjective)
			Headache (Headache temporal)
			Dry mouth (Dry mouth)
Day 9	36014	Asthenia (Fatigue)	
Day 6	79001	Abdominal pain (Abdominal pain)	
		Diarrhea (Diarrhea)	

MO Comment: All of the above adverse events were self-limiting and resolved following discontinuation of study drug.

The following table from the study report (Volume 237, page 127) shows clinically significant lab changes (as defined by the sponsor in the table)

Numbers of patients with clinically significant changes in selected laboratory values

Laboratory value	Criterion	BAY 12-8039 n = 245		Cefuroxime-axetil n = 251	
		n	%	n	%
Hematocrit	Decrease of $\geq 20\%$	0	0	1	0.4
Hemoglobin	Decrease of ≥ 2 g/dl	2	0.8	3	1.2
Platelet count	Decrease $\geq 25\%$	13	5.3	9	3.6
Serum creatinine	Increase ≥ 0.6 mg/dl	1	0.4	1	0.4
AST	Increase $\geq 100\%$ and ≥ 10 U/l	6	2.4	4	1.6
ALT	Increase $\geq 100\%$ and ≥ 10 U/l	2	0.8	10	4.0
Alk. Phosphatase	Increase $\geq 50\%$ and ≥ 50 U/l	1	0.4	2	0.8
Bilirubin, total	Increase $\geq 200\%$	2	0.8	1	0.4

MO Comment: Overall, moxifloxacin and cefuroxime had similar profiles with respect to the incidence of laboratory abnormalities. None of the patients in either treatment arm discontinued due to laboratory abnormalities.

C. Medical Officer 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 at various study sites throughout Europe. The design of the study poses several problems. The sponsor chose a test of cure window of 4 to 7 days post-therapy, while the FDA recommends a minimum of seven days off therapy before assessment of a test of cure clinical response. Secondly, microbiological efficacy data was mainly obtained via middle meatal [redacted] and the FDA currently accepts neither of these techniques for microbiological documentation of infection. Finally, as noted in the review for Protocol 100107, the medical reviewer is concerned that the inclusion criteria in the protocol could allow inclusion of patients with allergic rhinitis or viral upper respiratory tract infection. The FDA analysis attempted to address these problems as described below.

According to the sponsor, the clinical efficacy rates at the test of cure visit (Day +4 to +7 post-therapy) were 93.5% and 94.6% for the per protocol moxifloxacin and cefuroxime treatment arms, respectively; 95% C.I. = (-5.5%, 3.4%). For the all-treated patients population, the sponsor's response rates were 91% in both treatment arms; 95% C.I. (-5.2%, 4.8%). These results meet the protocol-defined criteria for clinical equivalence ($\delta = 0.15$). Bacteriological efficacy data suggests excellent activity of both

treatment arms against the three major pathogens in acute sinusitis, but the technique of specimen collection is unacceptable to support bacteriological efficacy for this indication in the NDA.

The FDA analysis used the followup visit (Day +27 to +31 post-therapy) as the test of cure visit to allow sufficient time off therapy to assess treatment response. The FDA per protocol population required either purulent nasal discharge and/or malar tenderness/pain to be present at baseline to enhance the likelihood of acute bacterial sinusitis in evaluable patients. Furthermore, the FDA definition of cure required at least improvement of these two "cardinal" symptoms of acute sinusitis at the test of cure visit. Response rates for moxifloxacin and cefuroxime at the test of cure visit were 87.1% and 88.8%, respectively; 95% C.I. = (-8.3%, 5.0%). Again, protocol-defined criteria for equivalence are met.

Drug-related adverse events occurred slightly more commonly in the moxifloxacin group (26.5%) compared to the control group (21.9%), and were mainly related to the gastrointestinal (nausea, diarrhea, abdominal pain) system. The incidence of laboratory abnormalities was similar between the two treatment arms.

- 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.

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ON ORIGINAL**

IV. Study 0116 (BAY 12-8039): "PROSPECTIVE, RANDOMISED, DOUBLE-BLIND, MULTI-CENTRE, MULTI-NATIONAL CLINICAL TRIAL COMPARING THE SAFETY AND EFFICACY OF BAY 12-8039 WITH CEFUROXIME-AXETIL IN THE TREATMENT OF PATIENTS WITH ACUTE SINUSITIS"

A. Overview

1. Objectives:

- To compare the safety and efficacy of oral BAY 12-8039 at 400 mg q.d. for seven days versus cefuroxime-axetil 250 mg b.i.d. for 10 days in the treatment of adult patients with clinically suspected acute bacterial sinusitis.

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

The rationale for proposing a 7-day duration of therapy based on pharmacokinetic, pharmacodynamic or other factors was not clearly presented in the protocol. The current medical literature generally recommends at least a ten day course of antimicrobial therapy for this closed space infection⁷. Treatment for shorter periods of time raises concerns regarding undertreatment of infection leading to post-therapy relapse infections.

2. Design

This was a prospective, two-armed, randomized, multi-center, double-blind, parallel-group, active controlled clinical trial in out-patients with acute bacterial sinus infections.

3. Inclusion Criteria

- Outpatients, at least 18 years of age.
- In female patients of child-bearing age, adequate contraception.
- Acute bacterial sinusitis, either bacteriologically documented or clinically suspected on the basis of radiological paranasal sinus x-ray occipitomeatal revealing air-fluid levels, opacification or ≥ 6 mm mucosal thickening.
- At least two of the following symptoms: nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar tenderness/pain, purulent nasal drainage.
- Willingness and ability to sign an informed consent form.

4. Exclusion Criteria:

- Age below 18 years.
- A history of hypersensitivity to either of the study drugs or related compounds.
- Severe cardiac failure (class IV of the NYHA classification).
- Having received a systemic antibacterial agent within 48 hours of enrolment, unless the patient was a clear clinical failure.
- Known renal insufficiency (serum creatinine > 265 µmol/l).
- Requirement for any concomitant systemic antibacterial agent.
- Previous sinus surgery (antral sinus puncture not considered as surgery).
- A history of chronic sinusitis with more than four weeks of continuous symptoms.
- Recurrence of more than two documented episodes of acute sinusitis within the previous six months.
- For female patients: pregnancy, lactation or use of inadequate contraception. (Note: Female patients of child-bearing potential must give a negative serum pregnancy test – negative urine test before enrolment to be confirmed by serum test – unless they had been surgically sterilised).
- Neutropenia (neutrophil count < 1000/mm³) due to malignancy or chemotherapy.
- Known liver disease or significant liver impairment (ALT/AST and/or baseline bilirubin above three times upper normal limit).
- Known or suspected bacteraemia or meningitis, including infiltrated neighbouring tissue of the sinus.
- Known AIDS (guideline, where available, CD4 count below 200/mm³).
- Severe infection requiring parenteral antimicrobial therapy or mechanical ventilatory support.
- Previous history of tendinopathy with fluoroquinolones.
- Participation in a clinical trial within the previous three months.
- Previous enrolment in this study.

MO Comment: The inclusion/exclusion criteria are generally acceptable for defining an adult patient population with uncomplicated, acute maxillary sinusitis. However, the reviewer notes the following:

- While the criteria specify that signs and symptoms at presentation should not exceed 4 weeks (to avoid enrollment of patients with subacute or chronic sinusitis), no minimum duration of signs and symptoms is required. The draft DAIDP Evaluability Criteria Guidance document recommends that symptoms be present for at least seven days to minimize the enrollment of patients with viral URI in clinical trials for acute bacterial sinusitis.
- The draft FDA Evaluability Criteria Guidance document 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

Acute Sinusitis Indication

three of these symptoms (nasal congestion, post-nasal drainage, and frequent coughing or throat clearing) are nonspecific for acute bacterial infection and are also manifestations of allergic rhinitis or viral URI. 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 of their symptoms.

- With respect to radiological diagnosis, both CT scan and plain films are acceptable modalities for documenting acute sinusitis. Most published studies and guidelines use the cutoff of 6 mm of mucosal thickening as supportive of a diagnosis of acute sinusitis.

5. Randomization/Blinding

Each center was supplied with sequentially numbered blister packs containing capsules for 10 days. The packaging and encapsulation of the trial drug (BAY 12-8039 400 mg), the comparator (cefuroxime-axetil 250 mg) and the placebo were such that all three appeared identical. The contents of the packs (moxifloxacin + placebo or cefuroxime-axetil) were pre-determined by a computer-generated randomization list prepared in advance at Bayer. In this way, the dispensation of drug supply to each patient at his/her enrolment provided automatically for randomization of the patient to one or the other treatment group.

MO Comment: The study was adequately randomized and blinded.

6. Study Procedures/ Observations

The following table summarizes the study procedures and patient assessments during the trial (from the NDA, Volume 242, pg. 40):

**APPEARS THIS WAY
ON ORIGINAL**

Study flow chart.

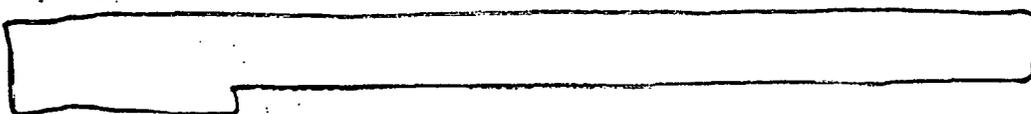
Procedure ↓	Activity →	Screening	Dosing	Evaluation		
	When performed →			One visit during dosing	One visit after dosing	One follow-up visit
		See note 1	Days 1-10	Days 7-9	Day 14	Days 37-41
Recording of medical history		+				
Assessment of patient eligibility		+				
Physical examination		+				
Signed informed consent		+				
Clinical signs/vital signs		+		+	+	+
Microbiological culture and susceptibility test (puncture, cannulation or swab)		+			+	+ 2
Occipitontental radiography		+			+ 3	
Haematology		+		+ 4		
Blood chemistry/urinalysis		+		+ 4		
Clinical evaluation				+	+	+
Monitoring of adverse events				+	+	
Drug intake (out-patient basis)			+ 5			

- 1 Screening was to take place no more than 48 hours before commencement of dosing on day 1.
- 2 Recommended in case of relapse.
- 3 Optional
- 4 Tests that yielded abnormal results considered potentially related to the study drug were to be repeated at appropriate intervals during follow-up to assess reversibility of the abnormalities.
- 5 EITHER BAY 12-8039 on days 1-7 and placebo on days 8-10, OR cefuroxime-axetil on days 1-10.

MO Comments:

Refer to MO Comments under the Study Procedures section for Protocol 0161.

Briefly:



- The test of cure evaluation time window (4 days post-therapy) does not allow sufficient time off study drug to assess efficacy. A time window of only one day in length is unrealistic.
- The draft ODE IV evaluability criteria guidance document recommends a followup radiological study (preferably the same modality used during the screening visit) at the test of cure visit. Patients should have no worsening of the post-therapy exam compared to the screening exam to be considered a "cure."

7. Evaluability Criteria

MO Comment: The evaluability criteria are identical to those in Protocol 0161 (refer to review above) and are acceptable.

8. Statistical Analyses

Sample Size Determination

The sample-size calculation assumed: a failure rate of 10–20% in the control group, an equivalence (clinically relevant) δ of 15%, $\alpha = 2.5\%$ (one-sided) and $\beta = 10\%$ (obtained at a failure rate of 20% in the BAY 12-8039 group). With an assumed validity rate of about 85%, 230 patients should be recruited in each treatment group, implying a total of at least 460 patients recruited.

Efficacy

The primary efficacy comparison was prospectively defined as comparison of the clinical responses at the end of therapy (Day +4 post-therapy) in the valid per protocol population to prove the hypothesis that the BAY 12-8039 therapy is not less effective than the cefuroxime-axetil therapy. If, and only if, the lower limit of the 95% confidence interval for the difference of the two clinical success rates (BAY 12-8039 minus cefuroxime-axetil) is greater than -15% , BAY 12-8039 therapy is proven to be not less effective than the cefuroxime-axetil therapy.

As for the primary efficacy variable, 95% confidence intervals for the following secondary efficacy variables (for the valid per-protocol population and for the intent-to-treat population) were calculated: the clinical response at days 27–31 (for both approaches as mentioned above) and the bacteriological response at the end of therapy.

Safety

For the safety analysis, the incidence and severity of adverse events and abnormal laboratory parameters were examined. The incidence rates of adverse events in the treatment groups were compared descriptively. Safety analysis included tabulation of the type and frequency of all AEs as well as events considered by the investigator to be at least possibly drug-related. All laboratory data were analysed by descriptive statistics including identification of laboratory data outside normal ranges.

B. Study Results

A total of 498 patients were enrolled in the trial: 244 patients in the moxifloxacin arm and 254 patients in the cefuroxime arm. According to the sponsor's analysis, 211 (86%) moxifloxacin-treated patients and 225 (90%) cefuroxime-treated patients were evaluable for the per protocol analysis. Patients were enrolled from 49 centers in six European countries and Israel. See Appendix III of this review for a listing of enrollment by study center and treatment arm.

MO Comment: As shown in Appendix III, the percentage of enrolled subjects who were considered evaluable for the per protocol analysis was high and consistent across treatment centers.

1. Demographics

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

**Demography, Per Protocol Population
 Study 0116**

Characteristic	Moxifloxacin N = 211	Cefuroxime-axetil N = 225
<u>Gender [N (%)]</u>		
Male	97(46.0)	99 (44.0)
Female	114(54.0)	126(56.0)
<u>Race [N (%)]</u>		
Caucasian	143 (67.8)	155 (68.9)
Not Reported	68 (32.2)	70 (31.1)
<u>Age</u>		
Mean	39.6	39.9
Median	37	37
Min. - Max.	18-82	18-85
<u>Weight (kg)</u>		
Mean	70.8	69.5
Median	69	67
Min. - Max.	44-155	41-117

MO Comment: Patient randomization for the study resulted in very comparable demographic characteristics for the two treatment arms for the per protocol population. The population was homogenous with respect to race (all Caucasian). Race was not reported for patients at French study sites due to legal reasons.

2. Reasons for Nonevaluability

As shown in the following table from the NDA (Volume 242, page 62), 62 patients were excluded from the per protocol population (33 moxifloxacin-treated patients and 29 cefuroxime-treated patients). The most common reasons were insufficient duration of therapy and violations of the inclusion/ exclusion criteria.

Non-validity for inclusion in the PP population (all patients enrolled)

	BAY 12-8039 N = 244		Cefuroxime-axetil N = 254		All patients N = 498	
	n	%	n	%	n	%
Any reason (a)	33	13.5	29	11.4	62	12.4
Insufficient duration of therapy	12	4.9	9	3.5	21	4.2
Violation of in-/exclusion criteria	10	4.1	8	3.1	18	3.6
Essential data missing/invalid	9	3.7	5	2.0	14	2.8

a) p-value of 0.49 for difference between treatment groups.

MO Comment: The reasons for exclusion from the per protocol population are consistent with the per protocol evaluability criteria and do not appear biased by treatment arm.

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

3. Description of Current Infection/Prognostic Factors

The following table was obtained from the NDA (Volume 237, page 286):

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DESCRIPTION OF ACUTE SINUSITIS
POPULATION: ALL PATIENTS VALID PER PROTOCOL

		TREATMENT GROUP						P-VALUE OF GROSS HOMOGENEITY
		MAY 17-2009 400 mg (MOXIFL)		CEPHALOSPORIN AZITRO-MYING (M-CZ)		ALL TREATMENT GROUPS COMBINED (N=418)		
		N	%	N	%	N	%	
ONSET OF PRESENT EPISODE (PRIOR THERAPY)	0 - <4 DAYS	71	33.6	70	34.7	149	34.2	
	4 - <7 DAYS	48	22.7	54	25.8	106	24.3	
	>= 7 DAYS	91	43.1	86	38.2	177	40.4	
	NOT REPORTED	1	0.5	3	1.3	6	0.9	
LOCATION OF PRESENT INFECTION (IF MULTIPLE AND/OR POSSIBLE)	FRONTAL	30	14.2	38	16.9	68	15.6	
	MAXILLARY LEFT	40	20.4	52	23.1	112	25.7	
	MAXILLARY RIGHT	52	24.6	66	29.3	118	27.1	
	MAXILLARY BILATERAL	55	45.0	101	44.9	196	45.0	
	ETHMOID LEFT	4	1.9	8	3.6	12	2.8	
	ETHMOID RIGHT	6	3.0	4	1.8	10	2.3	
	ETHMOID BILATERAL	15	7.1	12	5.3	27	6.2	
	SPHENOID LEFT	1	0.5			1	0.2	
SPHENOID BILATERAL	1	0.5	3	1.3	4	0.9		
NUMBER OF INVOLVED SINUSES	>=2	101	45.8	105	46.7	206	46.2	0.7617
	>2	37	16.2	30	13.3	60	13.8	
SEVERITY OF PRESENT INFECTION	MILD	13	6.2	12	5.3	25	5.7	0.0718
	MODERATE	112	52.1	143	63.6	255	58.5	
	SEVERE	81	40.8	70	31.1	156	35.8	
NO. OF EPISODES IN THE LAST 6 MONTHS	0	175	82.9	167	82.2	362	81.0	
	1	31	14.7	26	11.6	57	12.1	
	2	5	2.4	12	5.3	17	3.8	
	> 2							

MIO Comment: The groups were very comparable with respect to location of infection although the moxifloxacin patients had a higher percentage of severe infections than the control arm. It is unlikely that many patients with underlying chronic sinusitis or recurrent acute sinusitis were enrolled since most patients reported no sinus infections in the last 6 months.

4. Pretreatment Signs/Symptoms

MIO Comment: The groups were very comparable with respect to location of infection although the moxifloxacin patients had a higher percentage of severe infections than the control arm. It is unlikely that many patients with underlying chronic sinusitis or recurrent acute sinusitis were enrolled since most patients reported no sinus infections in the last 6 months.

4. Pretreatment Signs/Symptoms

The following table was obtained from the NDA (Volume 237, page 330):

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NDA # 21-085
Acute Sinusitis Indication

NDA # 21-061
Acute Sinusitis Indication

The following table was obtained from the NDA (Volume 237, page 330):

CLINICAL SIGNS AND SYMPTOMS AT STUDY ENTRY (PER PROTOCOL POPULATION)

		TREATMENT GROUP						P-VALUE OF DIFFERENCE OF HOMOGENEITY
		BAY 17-8039 (N=111)		CELESTON (N=111)		ALL TREATMENT GROUPS COINED (N=111)		
		N	%	N	%	N	%	
FRONTAL TENDRNESS	NONE	54	25.6	57	25.3	111	25.5	0.3097
	MILD	38	17.1	42	18.7	78	17.9	
	MODERATE	64	31.3	80	35.6	144	32.5	
	SEVERE	55	26.1	48	20.4	101	23.2	
NASAL TENDRNESS / PAIN	NONE	42	19.9	36	16.0	78	17.9	0.4473
	MILD	32	15.2	46	20.8	78	17.9	
	MODERATE	86	45.5	102	45.3	188	45.6	
	SEVERE	41	19.4	41	18.2	82	18.8	
NASAL CONGESTION	NONE	8	3.8	11	4.9	19	4.4	0.6904
	MILD	25	11.8	29	12.9	54	12.4	
	MODERATE	103	48.8	116	51.6	219	50.3	
	SEVERE	75	35.3	89	39.7	164	37.0	
POST-NASAL DRAINAGE / ITCHING	NONE	31	14.7	38	16.9	69	15.8	0.8831
	MILD	32	14.6	36	16.0	68	15.4	
	MODERATE	81	43.2	99	44.0	180	43.6	
	SEVERE	37	17.5	38	16.9	75	17.2	
COLD / NOSE CLEANING	NONE	72	33.4	83	36.9	154	35.3	0.1647
	MILD	56	26.3	66	29.3	122	28.0	
	MODERATE	70	32.2	54	24.0	124	28.4	
	SEVERE	18	8.4	22	9.8	36	8.3	
PURULENT NASAL DRAINAGE	NONE	15	7.1	21	9.2	36	8.2	0.4032
	MILD	67	22.3	38	16.9	85	19.3	
	MODERATE	100	47.4	109	48.4	209	47.9	
	SEVERE	69	23.2	55	24.4	104	23.9	

MO Comment: The treatment groups were well balanced with respect to baseline symptoms by severity.

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5. Reasons for Discontinuations

The following table was obtained from the NDA (Volume 242, page 60):

Number of discontinuations (all patients enrolled)

	BAY 12-8039 N = 244		Cefuroxime-axetil N = 254		All patients N = 498	
	n	%	n	%	n	%
Any reason	16	6.6	16	6.3	32	6.4
Adverse event	14	5.7	11	4.3	25	5.0
Consent withdrawn	3	1.2	3	1.2	6	1.2
Insufficient efficacy	0	0.0	1	0.4	1	0.2
Lost to follow-up	0	0.0	2	0.8	2	0.4
Non-compliance	0	0.0	1	0.4	1	0.2

Note that for a given patient more than one reason may apply.

MO Comment: The patient designated as "insufficient efficacy" received less than the required three days of therapy and thus could not be designated a treatment failure. Discontinuation were most commonly due to adverse events in both treatment arms.

6. Radiographic Findings

The following table from the NDA (Volume 242, page 250) summarizes the abnormal radiological findings in the all-treated patient population:

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ON ORIGINAL**

RESULTS OF RADIOLOGICAL PROCEDURES AT ENROLLMENT
 POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS
 REGION: ALL REGIONS

TRIMUS)	DESCRIPTION OF INT. RADIOLOGICAL FINDINGS (1)	TREATMENT GROUP					
		RAY 13-8039 400 MG (N=242)		CEFTROXIME- AXETIL 500MG (N=251)		ALL TREATMENT GROUP COMBINED (N=493)	
		NUMBER	%	NUMBER	%	NUMBER	%
	NORMAL OR NORMAL LIKE FOR PATIENT	3/242	1.2	3/251	1.2	6/493	1.2
	PATHOLOGICAL	235/242	97.1	248/251	98.8	483/493	98.0
	NOT REPORTED	4/242	1.7			4/493	0.8
	< 6MM MUCOPERIOSTEAL THICKENING	5/235	2.1	1/248	0.4	6/483	1.2
	MUCOPERIOSTEAL THICKENING >=6MM	114/235	48.5	119/248	48.0	233/483	48.2
	OPACIFICATION	130/235	55.3	138/248	55.6	268/483	55.5
	AIR-FLUID LEVEL	63/235	26.8	59/248	23.8	122/483	25.3
	POLYPOID MASSES			1/248	0.4	1/483	0.2

MO Comment: The [redacted] similar in pathological findings consistent with acute sinusitis. The medical officer verified that the 6 patients with normal [redacted] were not included in the per protocol population. The patients under the "Not Reported" category for [redacted] had [redacted] of infection.

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7. Study Drug Exposure

Refer to NDA Table 14.4.1/2 for complete details of study drug usage. Compliance with both treatment regimens was good: 98.6% of moxifloxacin-treated patients and 98.7% of cefuroxime-treated patients in the per protocol population received between 14 and 20 doses of study medication.

8. Efficacy

Clinical Efficacy

The following table summarizes the sponsor's evaluation of clinical response:

**Clinical Efficacy of Moxifloxacin and Cefuroxime in Acute Sinusitis
at the Test of Cure Visit (per Sponsor)
Study 0116**

Drug	Per Protocol Patients		All-Treated Patients	
	Efficacy Rate	95% C.I.	Efficacy Rate	95% C.I.
Moxifloxacin	96.7% (204/211)	(1.5, 10.6)	89.3% (216/242)	(-3.7, 7.8)
Cefuroxime	90.7% (204/225)		87.3% (219/251)	

MO Comments: Efficacy rates at the sponsor's test of cure visit (Day +4 post-therapy) tended to be higher in the moxifloxacin treatment arm across study sites, particularly in the southern Europe/Israel region (refer to NDA table 14.2.1/2.1). The 95% confidence intervals meet the protocol-specified criteria for clinical equivalence to cefuroxime in both the per protocol and all-treated patients populations. Although the confidence interval does not cross zero for the per protocol population, this study was not prospectively designed to establish superiority of moxifloxacin over cefuroxime and thus cannot be used to support such a claim.

As previously described, the FDA evaluable population had to have at least one of the "cardinal" symptoms of acute sinusitis at baseline (i.e., malar pain/tenderness or purulent nasal discharge). Consistent with the sponsor's definition of cure, these symptoms had to be resolved or improved at the test of cure visit to consider the patient a clinical cure. To allow adequate time off therapy to assess treatment response, the FDA analysis used the followup visit (Day +27 to +31 post-therapy) as the test of cure visit. As shown in the table below, the response rates for both treatment arms are lower compared to the sponsor's analysis. However, the confidence interval still easily meets the protocol-defined criteria for equivalence. The medical officer agrees that the efficacy data (by both FDA and sponsor's analysis) support clinical equivalence of the two treatment arms.

**Clinical Efficacy of Moxifloxacin and Cefuroxime in Acute Sinusitis
in Clinically Evaluable Patients (per MO) at Test of Cure Visit
Study 0116**

Drug	Per Protocol Patients	
	Efficacy Rate	95% C.I.
Moxifloxacin	87.0% (180/207)	(-1.6%, 13.2%)
Cefuroxime	81.2% (177/218)	

Bacteriological Efficacy

The majority of patients had bacteriological documentation of infection by [redacted] neither of these techniques is currently acceptable to the FDA for documentation of microbial etiology. As shown in the NDA table below (Volume 242, page 84), bacteriological success rates were high in both treatment arms:

Bacteriological responses by patient at the end of therapy (EOT)

Bacteriological response	BAY 12-8039 (N = 109)		cefuroxime-axetil (N = 115)	
	N	%	N	%
Bacteriological success rate	103	94.5%	96	83.5%
Eradication	41	37.6%	33	28.7%
Presumed eradication	62	56.9%	63	54.8%
Bacteriological failure rate	6	5.5%	19	16.5%
Eradication with superinfection	2	1.8%	7	6.1%
Persistence (1)	2	1.8%	7	6.1%
Presumed persistence	2	1.8%	5	4.3%

1) Including persistence with superinfection

Eradication or Presumed Eradication Rates for moxifloxacin-treated patients for the three major sinusitis pathogens in the microbiologically evaluable population were as follows:

Organism	Eradication/Presumed Eradication [N/Total Number of Organisms (%)]
<i>Streptococcus pneumoniae</i>	38/39 (97.4)
<i>Haemophilus influenzae</i>	29/29 (96.6)
<i>Moraxella catarrhalis</i>	14/14 (100)

MO Comment: Eradication rates for the three major pathogens were excellent. The methodology used for obtaining most culture specimens is unacceptable to the FDA for documenting microbiological efficacy of moxifloxacin. Study D94-023 used antral taps for documentation and was designed to demonstrate the activity of moxifloxacin against the three major pathogens above for the NDA.

9. Safety

Deaths

No deaths were reported in this study.

Serious Adverse Events

Eleven serious events occurred during the study, 3 in the moxifloxacin group and 8 in the cefuroxime axetil group. None of the moxifloxacin events were considered related to study drug therapy while two patients (one with bloody diarrhea and postural hypotension and one with headache/vomiting) were considered at least remotely possibly related to cefuroxime therapy. The moxifloxacin serious adverse events are summarized below:

Treatment group	Day started	Patient no.	Relationship to study drug	COSTART term (investigator's term)	Outcome
BAY 12-8039:					
	+18	493	none	Depression (depression)	Improved
	+25	325	none	Surgery (hospitalisation for sinus drainage)	Resolved
	+44	287	none	Accidental injury (trauma of knee)	Resolved

MO Comment: The medical officer confirmed that patient 325 was designated as a clinical failure in the efficacy analysis.

All Adverse Events

The following table from the NDA (Volume 242, page 101) shows adverse events with an incidence of at least 5% in either treatment arm without respect to causality:

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Adverse events (ITT population) recorded in at least 5 % of either treatment group

Body system (any event)	Most frequent AEs	BAY 12-8039 N = 242		Cefuroxime-axetil N = 251		All patients N = 493	
		n	%	n	%	n	%
Any system	Any AE	105	43.4	88	35.1	193	39.1
Body as a whole		32	13.2	32	12.7	64	13.0
	Abdominal pain	11	4.5	10	4.0	21	4.3
	Headache	8	3.3	5	2.0	13	2.6
Digestive system		54	22.3	38	15.1	92	18.7
	Diarrhea	27	11.2	15	6.0	42	8.5
	Nausea	10	4.1	6	2.4	16	3.2
	Vomiting	8	3.3	4	1.6	12	2.4
Nervous system		19	7.9	5	2.0	24	4.9
	Vertigo	7	2.9	2	0.8	9	1.8
Respiratory sys.		22	9.1	18	7.2	40	8.1
	Rhinitis	8	3.3	5	2.0	13	2.6

MO Comment: The rate of adverse events tended to be slightly higher across body systems for the moxifloxacin group. The majority of adverse events in both groups were related to the digestive system with nausea, diarrhea and abdominal pain slightly more common in the moxifloxacin arm.

The following table from the study report (Volume 242, page 102) shows drug-related adverse events:

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**Adverse Events Rated as at least Remotely Drug-Related
Study 0116 (ITT population)**

Body system (any event)	Most frequent AEs	BAY 12-8039 N = 242		Cefuroxime-axetil N = 251		All patients N = 493	
		n	%	N	%	n	%
Any system	Any AE	76	31.4	58	23.1	134	27.2
Body as a whole		22	9.1	18	7.2	40	8.1
	Abdominal pain	10	4.1	7	2.8	17	3.4
	Headache	3	1.2	3	1.2	6	1.2
Digestive system		48	19.8	35	13.9	83	16.8
	Diarrhea w. bleeding	0	0.0	2	0.8	2	0.4
	Diarrhea	23	9.5	15	6.0	38	7.7
	Nausea	9	3.7	5	2.0	14	2.8
	Nausea and vomiting	3	1.2	3	1.2	6	1.2
	Vomiting	8	3.3	4	1.6	12	2.4
Nervous system		15	6.2	4	1.6	19	3.9
	Vertigo	7	2.9	2	0.8	9	1.8
	Dizziness	3	1.2	1	0.4	4	0.8

MO Comment: The overall rate of drug-related adverse events was higher for the moxifloxacin arm compared to the cefuroxime arm. Fourteen patients in the moxifloxacin arm and eleven patients in the cefuroxime arm discontinued due to adverse events. As shown in the summary below (Volume 242, page 109), most moxifloxacin discontinuations were due to gastrointestinal complaints, although three patients may have had Type I hypersensitivity reactions (pruritis). Patient #78 was mislabeled as "Shock (circulatory failure)." On the second day of treatment this patient developed diarrhea, hot flashes, malaise, weakness, and orthostatic symptoms which lasted three days. These events were considered not serious, and the patient was not hospitalized.

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Adverse events leading to discontinuation of therapy

Treatment group	Day started	Patient no.	COSTART term (investigator's term)
BAY 12-8039			
	Day 2	78	Shock (circulatory failure) and diarrhoea (diarrhoea)
		333	Dizziness (complained of dizzy and light-headed feeling for three minutes) and diarrhoea (diarrhoea)
	Day 3	97	Pruritus (pruritus)
		148	Abdominal pain (stomach ache)
		251	Vertigo (vertiginous sensations), nausea and vomiting (Nausea and vomiting), headache (light headache) and malaise (general malaise)
		288	Vomiting (vomit)
		303	Diarrhoea (diarrhoea)
		318	Anxiety (stress anxiety), depersonalisation (drunk feeling) Insomnia (insomnia) and diarrhoea (light diarrhoea)
		460	Nausea and vomiting (nausea and vomiting)
		614	Headache (headache) and vomiting (vomiting)
		626	Allergic reactions (allergic reaction on skin)
	Day 4	274	Pruritus (scratchy hair) and nausea (nausea)
	Day 7	196	Diarrhoea (diarrhoea increased frequency)
		277	Gastrointestinal disorder (digestive disorder).

The following table from the study report (Volume 242, page 112) shows clinically significant lab changes (as defined by the sponsor in the table):

Numbers of patients with clinically significant changes in selected laboratory values

Laboratory value	Criterion	BAY 12-8039		Cefuroxime-axetil	
		N = 242		N = 251	
		n	%	n	%
Platelet count	Decrease $\geq 25\%$	23	9.5	26	10.3
Serum creatinine	Increase ≥ 0.6 g/l	-	0.0	-	0.0
AST	Increase $\geq 100\%$ and 10 U/l	3	1.2	3	1.1
ALT	Increase $\geq 100\%$ and 10 U/l	5	2.0	9	3.5
Alk. Phosphatase	Increase $\geq 50\%$ and 50 U/l	-	0.0	4	1.5

MO Comment: Overall, moxifloxacin and cefuroxime had similar profiles with respect to the incidence of laboratory abnormalities. Liver function test abnormalities tended to be more frequent among cefuroxime-treated patients. None of the patients discontinued due to laboratory abnormalities.

C. Medical Officer Summary/Conclusions

This prospective, randomized study compared the safety and efficacy of moxifloxacin 400 mg po qd for seven days to cefuroxime 250 mg po bid for 10 days in patients with acute sinusitis at various study sites throughout Europe. The medical officer noted very similar problems to those discussed in the review of Study 0161 above. Namely, the sponsor chose a test of cure window at 4 days post-therapy, while the FDA recommends a minimum of seven days off therapy before assessment of a test of cure clinical response. Secondly, microbiological efficacy data was mainly obtained [redacted] and the FDA currently accepts neither of these techniques for microbiological documentation of infection. Finally, as noted in the review for Protocol 100107, the medical reviewer is concerned that the inclusion criteria in the protocol could allow enrollment of patients with allergic rhinitis or viral upper respiratory tract infection. The FDA analysis attempted to address these problems as described below.

According to the sponsor, the clinical efficacy rates at the test of cure visit (Day +4 post-therapy) were 96.7% and 90.7% for the per protocol moxifloxacin and cefuroxime treatment arms, respectively; 95% C.I. = (1.5%, 10.6%). Although the confidence interval does not cross zero for the per protocol population, this study was not prospectively designed to establish superiority of moxifloxacin over cefuroxime and thus cannot be used to support such a claim. For the all-treated patients population, the sponsor's response rates were 89.3% and 87.3% in the moxifloxacin and cefuroxime arms, respectively; 95% C.I. = (-3.7%, 7.8%). These results meet the protocol-defined criteria for clinical equivalence ($\delta = 0.15$). Bacteriological efficacy data suggests excellent activity of both treatment arms against the three major pathogens in acute sinusitis, but the techniques of microbiological specimen collection were unacceptable to support bacteriological efficacy for this indication in the NDA.

The FDA analysis used the followup visit (Day +27 to +31 post-therapy) as the test of cure visit to allow sufficient time off therapy to assess treatment response. The FDA per protocol population required either purulent nasal discharge and/or malar tenderness/pain to be present at baseline to enhance the likelihood of acute bacterial sinusitis in evaluable patients. Furthermore, the FDA definition of cure required at least improvement of these two "cardinal" symptoms of acute sinusitis at the test of cure visit. Response rates for moxifloxacin and cefuroxime at the test of cure visit were 87.0% and 81.2%, respectively; 95% C.I. = (-1.6%, 13.2%). Again, protocol-defined criteria for equivalence are easily met.

Drug-related adverse events occurred slightly more commonly in the moxifloxacin group (31.4%) compared to the control group (23.1%), and were mainly related to the gastrointestinal (nausea, diarrhea, abdominal pain) system. The incidence of laboratory abnormalities was similar between the two treatment arms.

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.

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V. Study D96-023: "Prospective, uncontrolled, non-blind, clinical trial of the safety and efficacy of BAY 12-8039 400 mg PO once daily in the treatment of patients with acute bacterial maxillary sinusitis"

A. Overview

1. Objectives

- To evaluate the safety and efficacy of moxifloxacin administered 400 mg orally once daily for 7 days in the treatment of patients with acute bacterial maxillary sinusitis (primary objective).
- To gather a sufficient number of isolates of bacterial pathogens which commonly cause sinus infections by antral puncture (secondary objective).

MO Comments: The rationale for proposing a 7-day duration of therapy based on pharmacokinetic, pharmacodynamic or other factors was not clearly presented in the protocol. The current medical literature generally recommends at least a ten-day course of antimicrobial therapy for this closed space infection⁷. Treatment for shorter periods of time raises concern regarding undertreatment of infection leading to post-therapy relapse infections. However, if the sponsor is able to demonstrate acceptable activity against the major sinusitis pathogens after only seven days of therapy, this study should also support the proposed 10 day treatment regimen as well.

2. Design

This was a prospective, uncontrolled, non-blinded Phase III clinical trial designed to evaluate the safety and efficacy of moxifloxacin in the treatment of acute suspected bacterial maxillary sinus infections. Sinus aspiration was performed at baseline for all patients. Eligible patients received moxifloxacin orally at a dose of 400 mg administered once daily for 7 days. Safety and efficacy were assessed at the during-therapy visit (Days 3 to 5), at the end-of-therapy visit (2 to 4 days after the last dose of study drug), and at a follow-up visit (27 to 31 days after the last dose). Antimicrobial effectiveness was evaluated by assessment of clinical signs and symptoms of infection and by sinus x-ray. The microbiological effectiveness of moxifloxacin in eradicating *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, the pathogens usually associated with sinus infections (causative organisms), was determined.

3. Inclusion Criteria

MO Comment: Inclusion criteria are identical to those in Study 0161. Refer to MO Comments in the review of this study above.

4. Exclusion Criteria

MO Comment: Exclusion criteria are identical to those in Study 0161 (listed in the review of that study) and are acceptable.

5. Randomization/Blinding

MO Comment: Randomization and blinding procedures in this study were identical to those used in the preceding studies and were acceptable.

6. Study Procedures/ Assessments:

The following table from the NDA (Volume 234, page 50) summarizes the study procedures/assessments:

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Study Procedures

	Screening Visit ¹	During-Therapy Visit ¹	End-of-Therapy Visit ¹	Follow-up Visit ¹
Informed consent	✓			
Evaluate patient eligibility	✓			
Medical history	✓			
Physical examination	✓			
Sinus x-ray	✓	✓ ²	✓	✓ ³
Gram stain, culture, and susceptibility	✓	✓ ²	✓ ²	✓ ⁴
Clinical laboratory tests:				
Hematology, chemistry, urinalysis	✓	✓	✓ ⁵	
Theophylline level ⁶	✓	✓	✓	
Pregnancy test ⁷	✓		✓	
Clinical evaluation (symptoms and response to treatment)		✓	✓	✓
Bacteriological response			✓	✓
Assess compliance		✓	✓	
Record adverse events		✓	✓	✓

¹ Screening visit: no more than 48 hours before start of dosing; during-therapy visit: Day 3 to 5 of therapy; end-of-therapy visit: 2 to 4 days after the last dose of study drug; follow-up visit: 27 to 31 days after the last dose of study drug

² For patients considered therapeutic failures

³ Only if previous x-ray continued to show abnormalities

⁴ Antral cultures recommended for clinical relapses

⁵ In case of abnormal laboratory findings judged potentially related to the study drug, laboratory tests were to be repeated at appropriate intervals until the end of the study or until laboratory values returned to normal

⁶ Only in patients receiving theophylline concomitantly

⁷ Although a negative urine pregnancy test was sufficient for enrollment, a serum pregnancy test was required before treatment and end of therapy

MO Comment: The planned visits, assessments and procedures are acceptable. The end of therapy visit does not allow sufficient time off study drug to assess treatment response.

7. Evaluability Criteria:

Efficacy Evaluability Criteria

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

MO Comment: The efficacy evaluability criteria are acceptable. The original planned primary efficacy variable was clinical response at the end of therapy (Day +2 to +4) visit. Subsequently, the FDA released draft evaluability criteria guidelines for acute sinusitis. In response to these guidelines and during the conduct of the study, the sponsor changed the primary efficacy visit to the followup visit (Day 27-31 post-therapy). Prior to breaking the blind, this window was then extended to +21 to +37 days post-therapy to maximize the number of clinically evaluable patients.

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.

8. Statistical Analyses

Sample Size Determination

The planned sample size of 250 patients was based on the estimated number of patients needed to have a sufficient number with documented bacterial pathogens, (i.e., 25 isolates of *H. influenzae* and *S. pneumoniae*, and 15 isolates of *M. catarrhalis*), as it was expected that no pathogens would be isolated in about 50% of patients.

Efficacy Analyses

As discussed above, the primary efficacy variable was the clinical response at the 21-37 day post-therapy time window. The primary population for analysis was specified as the subset of patients considered clinically evaluable. A subset of patients considered clinically and microbiologically evaluable was also planned. Intent-to-treat (ITT) analyses were also planned for the demographic and efficacy variables. The protocol specified that a two-sided 95% confidence interval for the clinical success rate (resolution rate) would be constructed, using a normal approximation to the binomial distribution, with a continuity correction.

Safety

Refer to the safety analysis plan for the preceding studies.

B. Study Results

1. Patient Population

A total of 372 patients were enrolled in the trial at 25 study sites across the United States. According to the sponsor's analysis, 336 (90%) of moxifloxacin-treated patients were clinically evaluable for the efficacy analysis. See Appendix IV for a listing of enrollment by study center.

MO Comment: As shown in Appendix IV, the percentage of enrolled subjects who were considered evaluable for the per protocol analysis was high and generally consistent across treatment centers. However, the rates of microbiologically valid patients was much more variable. This finding may reflect differences in antral puncture technique, laboratory isolation techniques or differences in the microbiology of infection at the various study sites.

2. Demographics

The following table from the NDA (Volume 234, page 60) summarizes key demographic and baseline infection characteristics for the study population:

Key Demographic and Infection Characteristics
(per protocol population)

Demographic Characteristics:	Moxifloxacin (N = 336)
Sex	
Male	128 (38%)
Female	208 (62%)
Race	
White	282 (84%)
Black	28 (8%)
Asian	3 (<1%)
Hispanic	23 (7%)
Mean age at enrollment (years)	41.0
Mean weight (kg)	78.8
Infection characteristics:	
Location of infection	
Left	92 (27%)
Right	85 (25%)
Bilateral	159 (47%)
Severity of infection	
Mild	13 (4%)
Moderate	207 (62%)
Severe	116 (35%)

Excerpted from Table 14.1/4 and Table 14.1/5

MO Comment: Demographic and infection characteristics are very similar to those in the other comparator-controlled studies in the NDA.

3. Pretreatment Signs/Symptoms

From the NDA study report (Volume 234, page 61):

Severity of Primary Clinical Signs and Symptoms of Infection at Study Entry
(Per Protocol Population)

Sign/Symptom:	None ¹	Mild ¹	Moderate ¹	Severe ¹
Frontal headache	16%	16%	37%	31%
Malar tenderness/pain	16%	21%	41%	22%
Nasal congestion	3%	12%	46%	39%
Post-nasal drainage/discharge	5%	21%	42%	32%
Cough/throat clearing	12%	22%	45%	21%
Purulent nasal drainage	10%	16%	40%	35%

¹Percentage of 336 patients included in efficacy analysis.

Excerpted from Table 14.1/8

MO Comment: Baseline clinical signs/symptoms closely parallel those in the comparator-controlled trials in the NDA. The incidence of moderate and severe purulent nasal drainage and malar tenderness/pain (i.e. "cardinal" symptoms of acute sinusitis) was slightly greater in this study compared to other studies in the NDA.

4. Reasons for Nonevaluability

The following table is from the NDA (Volume 234, page 59):

Reasons for Exclusion from Efficacy Analysis	
Reasons for Exclusion:	BAY 12-8039 (N = 372)
Essential data missing or invalid	19
Violation of inclusion/exclusion criteria	8
Use of prohibited concomitant medications	4
Insufficient duration of therapy	3
Not treated (Patient 7016)	1
Non compliance with study drug regimen	1
Total number of patients excluded from efficacy analyses	36

Excerpted from Table 14.1/3

MO Comment: The reasons for exclusion from the per protocol population are consistent with the per protocol evaluability criteria. The medical officer verified that the 19 patients with "essential data missing or invalid" had a clinical response assessment outside the Day +21 to +37 time window. As in the review of Study 100107, the reviewer is concerned that the inclusion criteria as outlined in the protocol may have allowed inclusion of patients with conditions other than acute bacterial sinusitis. In order to lessen the likelihood of including patients with viral or allergic disease, the FDA per protocol population required at least one of the two "cardinal" signs/symptoms (purulent nasal discharge, malar pain/tenderness) rated by the investigators which are more indicative of acute bacterial sinusitis than viral or allergic disease.

5. 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	
	ITT N= 371	Eval = N= 336
Mucosal Thickening \geq 6 mm	206 (55.5)	187(55.7)
Opacification	155 (42.9)	145 (43.2)
Air/Fluid Level	174 (46.9)	160(47.6)

MO Comment: The medical officer's review of the baseline radiographic datasets revealed that all patients met radiographic criteria for enrollment in the study.

6. Study Drug Exposure

Refer to NDA Table 14.1.11 for complete details of study drug usage. Compliance with both treatment regimens was excellent: 99% of moxifloxacin-treated patients in the per-protocol population received 6 or 7 doses of study medication.

7. Efficacy

Clinical Efficacy

The following table summarizes the sponsor's evaluation of clinical response for the per protocol and ITT populations:

**Clinical Efficacy of Moxifloxacin in Acute Sinusitis
at the Test of Cure Visit (per Sponsor)
Study D96-023**

Population	Efficacy Rate	95% C.I.
Per Protocol (sponsor)	80% (270/336)	(76%, 84%)
Per Protocol (FDA)	76% (253/331)	(72%, 81%)
ITT	81% (289/357)	(77%, 85%)

MO Comments: Efficacy rates at the sponsor's test of cure visit (Day +21 to +37 post-therapy) were acceptable. As previously described, the FDA per protocol population had to have at least one of the cardinal symptoms of acute sinusitis at baseline (i.e., malar pain/tenderness or purulent nasal discharge). Consistent with the sponsor's definition of cure, these symptoms had to be resolved or improved at the test of cure visit to consider the patient a clinical cure. To allow adequate time off therapy to assess treatment response the FDA analysis used the followup visit (Day +27 to +31 post-therapy as the test of cure visit. The clinical response rate at the test of cure visit by both the FDA and sponsor's analysis was notably lower than that seen for Studies 100107, 0161, and 0116. This finding may be attributable to more severe baseline infections in this study population (see *Pretreatment Signs/Symptoms* section above), or the open-label, non-comparative design of this study.

Bacteriological Efficacy

The overall bacteriological efficacy rates for moxifloxacin at the end of therapy and followup visit were 97% (72/74) and 86% (64/74), respectively. The table below from the NDA (Volume 234, page 135) lists the rates of eradication, presumed eradication, indeterminate, and presumed persistence for the three major pathogens in acute sinusitis:

SUMMARY OF BACTERIOLOGICAL RESPONSES AT EOT AND FOLLOWUP BY ORGANISM
POPULATION: PATIENTS VALID FOR EFFICACY

TIMEPOINT		BAY 12-8039 400MG							
		ERADICATION		PRESUMED ERADICATION		INDETERMINATE		PRESUMED PERSISTENCE	
		N	%	N	%	N	%	N	%
END OF THERAPY	STREPTOCOCCUS PNEUMONIAE	1	3	29	97	0	0	0	0
	MORAXELLA CATARRHALIS	0	0	16	89	1	6	1	6
	HAEMOPHILUS INFLUENZAE	1	4	29	97	0	0	0	0
FOLLOWUP	STREPTOCOCCUS PNEUMONIAE	0	0	29	97	0	0	1	3
	MORAXELLA CATARRHALIS	0	0	15	83	0	0	3	17
	HAEMOPHILUS INFLUENZAE	0	0	24	80	0	0	6	20

MO Comment: MO analysis of the bacteriological datasets for this study produced very similar results to those in the table above. As the followup visit was considered as the test of cure visit in the final analyses, the eradication/presumed eradication rates for the three major pathogens is as follows:

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

MO analysis of the datasets showed the eradication/presumed eradication rates for penicillin-resistant (MIC ≥ 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 penicillin-resistant and intermediate susceptibility pneumococcal isolates obtained in this study limit the interpretation of these bacteriological efficacy rates. However, the data clearly support the sponsor's proposed labeling for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

8. Safety

Deaths

No deaths were reported in this study.

Serious Adverse Events

No serious adverse events were reported in this study.

All Adverse Events

A total of 118 of the 371 patients (51%) in the safety population experienced at least one adverse event. In 109 of these patients (29%), the event was considered to be related to study drug therapy. The following table from the NDA (Volume 234, page 69) shows adverse events with an incidence of at least 2% without respect to causality:

Adverse Events Occurring in at Least 2% of Patients (N = 371)

Adverse Event	BAY 12-8039
Any event	188 (51%)
Headache	37 (10%)
Pain	16 (4%)
Abdominal pain	7 (2%)
Hemorrhage	33 (9%)
Syncope	11 (3%)
Nausea	42 (11%)
Diarrhea	21 (6%)
Dyspepsia	9 (2%)
Dry mouth	7 (2%)
Vomiting	6 (2%)
Dizziness	14 (4%)
Insomnia	11 (3%)
Nervousness	6 (2%)
Hypesthesia	6 (2%)
Rhinitis	13 (4%)
Epistaxis	8 (2%)

MO Comment: All hemorrhage and syncopal events were due to the [redacted] Only two patients discontinued the study due to adverse events. One patient developed a facial cellulitis related to extravasation of lavage fluid into the soft tissues overlying the maxillary sinus during the [redacted] (not considered to be a drug-related adverse event). The other patient developed nausea, dizziness, dry mouth, and taste perversion 2 hours after taking her second dose of moxifloxacin and these events were judged to be probably related to study drug therapy.

Drug-related adverse events are displayed in the table below from the NDA (Volume 234, page 70):

Drug-Related Adverse Events Occurring in at Least 2% of Patients (N = 371)

Adverse Event	BAY 12-8039
Any event	109 (29%)
Headache	16 (4%)
Nausea	37 (10%)
Diarrhea	18 (5%)
Dyspepsia	8 (2%)
Dry mouth	7 (2%)
Dizziness	12 (3%)
Insomnia	8 (2%)

MO Comment: As in previously reviewed studies, drug-related adverse events were typically mild in severity and related to the gastrointestinal and nervous systems.

The following table from the study report (Volume 236, page 47) shows clinically significant lab abnormalities (per sponsor's definition) that occurred during the study:

CLINICALLY SIGNIFICANT CHANGES IN LABORATORY VALUES

POPULATION: PATIENTS VALID FOR ANALYSIS OF SAFETY

LABORATORY TEST	CLINICALLY SIGNIFICANT CHANGE FROM BASELINE	BAY 12-8039 400MG N TOTAL (%)
HEMATOLOGY		
HEMATOCRIT (%)	DECREASE OF 20 % FROM BASELINE	0 364 (0)
HEMOGLOBIN (G/DL)	DECREASE OF 2 FROM BASELINE	5 364 (1)
PLATELETS (PER CUMM)	DECREASE OF 25 % FROM BASELINE	18 364 (5)
BLOOD CHEMISTRY		
SGOT/AST (U/L)	INCREASE OF 100 % OVER BASELINE	8 367 (2)
SGPT/ALT (U/L)	INCREASE OF 100 % OVER BASELINE	18 367 (5)
SGOT/AST (U/L)	INCREASE OF 10 FROM BASELINE	23 367 (6)
SGPT/ALT (U/L)	INCREASE OF 10 FROM BASELINE	34 367 (9)
BILIRUBIN, TOTAL (MG/DL)	INCREASE OF 200 % OVER BASELINE	1 367 (0)
CREATININE (MG/DL)	INCREASE OF 50 % OVER BASELINE	4 367 (1)
	INCREASE OF 0.6 FROM BASELINE	0 367 (0)
BUN (MG/DL)	INCREASE OF 75 % OVER BASELINE	13 367 (4)
ALKALINE PHOSPHATASE (U)	INCREASE OF 100 % OVER BASELINE	1 367 (0)
	INCREASE OF 50 FROM BASELINE	1 367 (0)

MO Comments: No patients discontinued the study due to abnormal laboratory tests. Abnormal lab tests were uncommon and not linked to any apparent clinical adverse events.

C. Medical Officer Summary/Conclusions

This uncontrolled, open-label study assessed the safety and efficacy of moxifloxacin 400 mg administered orally once daily for 10 days in patients with acute sinusitis at various study sites throughout the United States. Unlike Studies 0161 and 0116, this study used only [redacted] to document microbial etiology of infection, and the microbiological data from this study is therefore acceptable to the FDA in support of the acute sinusitis indication. However, as noted in the review for Protocol 100107,