BAY 12-8039/D96-027
BRONCHITIS

APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
44	Barash	11FEB97	21FEB97	BAY 12-8039 400MG X 5	1	1	1	0	1
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	0	0	0	0	0
				TOTAL	1	1	1	0	1
45	Krumpe	18MAR97	26JUN97	BAY 12-8039 400MG X 5	2	2	2	0	2
				BAY 12-8039 400MG X 10	3	3	3	1	3
				CLARITHROMYCIN	2	2	2	0	2
				TOTAL	7	7	7	1	7
46	DeGraff	25MAR97	18SEP97	BAY 12-8039 400MG X 5	3	3	3	1	3
				BAY 12-8039 400MG X 10	1	1	1	1	1
				CLARITHROMYCIN	3	3	3	1	3
				TOTAL	7	7	7	3	7
47	Nelson	06JUN97	21DEC97	BAY 12-8039 400MG X 5	4	4	4	1	4
				BAY 12-8039 400MG X 10	4	4	3	2	4
				CLARITHROMYCIN	4	4	4	1	3
				TOTAL	12	12	10	4	11
48	Harless	09OCT97	12FEB98	BAY 12-8039 400MG X 5	8	8	5	4	8
				BAY 12-8039 400MG X 10	6	6	6	4	6
				CLARITHROMYCIN	7	7	3	2	7
				TOTAL	21	21	14	10	21
49	Green	28OCT97	23FEB98	BAY 12-8039 400MG X 5	2	2	0	0	1
				BAY 12-8039 400MG X 10	1	1	1	1	1
				CLARITHROMYCIN	1	1	1	0	1
				TOTAL	4	4	2	1	3
50	Fogarty	04SEP97	08MAR98	BAY 12-8039 400MG X 5	15	15	15	12	15
				BAY 12-8039 400MG X 10	14	14	13	7	13
				CLARITHROMYCIN	14	14	11	8	13
				TOTAL	43	43	39	27	41
51	Habib	05NOV97	02MAR98	BAY 12-8039 400MG X 5	5	5	4	2	5
				BAY 12-8039 400MG X 10	7	7	7	4	6
				CLARITHROMYCIN	4	4	3	2	3
				TOTAL	16	16	14	8	14

BAY 12-8039/D96-027
BRONCHITIS

APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
52	Weisman	23OCT97	14DEC97	BAY 12-8039 400MG X 5	1	1	0	0	1
				BAY 12-8039 400MG X 10	2	2	2	0	2
				CLARITHROMYCIN	1	1	1	0	1
				TOTAL	4	4	3	0	4
53	Henry	19SEP97	27FEB98	BAY 12-8039 400MG X 5	3	3	2	1	3
				BAY 12-8039 400MG X 10	4	4	4	4	4
				CLARITHROMYCIN	4	4	3	2	3
				TOTAL	11	11	9	7	10
54	Smith	04NOV97	27FEB98	BAY 12-8039 400MG X 5	2	2	1	0	1
				BAY 12-8039 400MG X 10	1	1	1	1	1
				CLARITHROMYCIN	0	0	0	0	0
				TOTAL	3	3	2	1	2
55	Pullman	24OCT97	01MAR98	BAY 12-8039 400MG X 5	5	5	5	5	5
				BAY 12-8039 400MG X 10	4	4	4	4	4
				CLARITHROMYCIN	4	4	4	3	4
				TOTAL	13	13	13	12	13
56	Van Hook	16SEP97	23FEB98	BAY 12-8039 400MG X 5	4	4	3	3	4
				BAY 12-8039 400MG X 10	4	4	2	1	2
				CLARITHROMYCIN	4	4	3	2	3
				TOTAL	12	12	8	6	9
57	Hall	24NOV97	07JAN98	BAY 12-8039 400MG X 5	1	1	0	0	1
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	1	1	1	1	1
				TOTAL	2	2	1	1	2
58	Spindel	18DEC97	27DEC97	BAY 12-8039 400MG X 5	1	1	1	1	1
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	0	0	0	0	0
				TOTAL	1	1	1	1	1
60	Fidelholtz	04FEB98	25FEB98	BAY 12-8039 400MG X 5	1	1	1	0	1
				BAY 12-8039 400MG X 10	1	1	0	0	1
				CLARITHROMYCIN	1	1	0	0	0
				TOTAL	3	3	1	0	2

BAY 12-8039/D96-027
BRONCHITIS

APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
ALL CENTERS		21NOV96	09MAR98	MOXIFLOXACIN X 5 DAYS	316	312	250	143	284
				MOXIFLOXACIN X 10 DAYS	307	302	256	148	277
				CLARITHROMYCIN	313	312	251	129	276
				TOTAL	936	926	757	420	837

BAY 12-8039/D96-022
BRONCHITIS

APPENDIX 2
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
1	Champlin	06JAN97	05MAR97	BAY 12-8039 200	4	4	1	0	4
				BAY 12-8039 400	4	4	3	1	3
				CEFUROXIME AXETIL	3	3	3	1	3
				TOTAL	11	11	7	2	10
2	Heyder	18DEC96	10MAY98	BAY 12-8039 200	32	32	28	9	28
				BAY 12-8039 400	32	32	28	5	30
				CEFUROXIME AXETIL	31	31	28	8	31
				TOTAL	95	95	84	22	89
3	Applestein	20NOV96	19JAN98	BAY 12-8039 200	3	3	3	1	3
				BAY 12-8039 400	3	3	3	1	3
				CEFUROXIME AXETIL	3	3	3	0	3
				TOTAL	9	9	9	2	9
4	Black	18NOV96	13FEB98	BAY 12-8039 200	4	4	4	0	4
				BAY 12-8039 400	5	5	3	0	4
				CEFUROXIME AXETIL	6	6	5	1	6
				TOTAL	15	15	12	1	14
5	Ervin	04FEB97	10MAR97	BAY 12-8039 200	2	2	2	0	2
				BAY 12-8039 400	0	0	0	0	0
				CEFUROXIME AXETIL	1	1	1	0	1
				TOTAL	3	3	3	0	3
6	Farrell	24JAN97	03AUG97	BAY 12-8039 200	3	3	3	0	3
				BAY 12-8039 400	4	4	3	0	4
				CEFUROXIME AXETIL	4	4	4	0	4
				TOTAL	11	11	10	0	11
7	Graff	09JAN97	17APR98	BAY 12-8039 200	5	5	5	3	5
				BAY 12-8039 400	6	6	4	2	5
				CEFUROXIME AXETIL	5	5	5	2	5
				TOTAL	16	16	14	7	15
9	Sokol	25NOV96	06MAR97	BAY 12-8039 200	4	4	2	0	3
				BAY 12-8039 400	4	4	2	0	4
				CEFUROXIME AXETIL	4	4	1	0	3
				TOTAL	12	12	5	0	10

BAY 12-8039/D96-022
BRONCHITIS

APPENDIX 2 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
10	Tucker	18DEC96	29JAN98	BAY 12-8039 200	4	4	4	4	4
				BAY 12-8039 400	4	4	3	2	4
				CEFUROXIME AXETIL	4	4	3	1	3
				TOTAL	12	12	10	7	11
11	Mogyoros	10FEB97	30APR97	BAY 12-8039 200	1	1	0	0	0
				BAY 12-8039 400	1	1	1	0	0
				CEFUROXIME AXETIL	1	1	1	1	1
				TOTAL	3	3	2	1	1
13	Anzueto	16MAY97	19MAY97	BAY 12-8039 200	0	0	0	0	0
				BAY 12-8039 400	1	1	0	0	0
				CEFUROXIME AXETIL	0	0	0	0	0
				TOTAL	1	1	0	0	0
14	Braverman	03JAN97	17MAR97	BAY 12-8039 200	4	4	4	0	4
				BAY 12-8039 400	4	4	3	0	3
				CEFUROXIME AXETIL	5	5	5	0	5
				TOTAL	13	13	12	0	12
15	Diller	07FEB97	11AUG97	BAY 12-8039 200	3	3	2	0	1
				BAY 12-8039 400	3	3	2	0	3
				CEFUROXIME AXETIL	4	4	1	0	3
				TOTAL	10	10	5	0	7
16	Interiano	06DEC96	24MAR98	BAY 12-8039 200	6	6	4	2	5
				BAY 12-8039 400	5	5	5	0	5
				CEFUROXIME AXETIL	4	4	2	0	2
				TOTAL	15	15	11	2	12
17	Kessler	07JAN97	14FEB98	BAY 12-8039 200	3	3	1	0	3
				BAY 12-8039 400	3	3	2	0	3
				CEFUROXIME AXETIL	4	4	3	0	3
				TOTAL	10	10	6	0	9
18	Munk	24JAN97	02APR97	BAY 12-8039 200	4	4	1	0	1
				BAY 12-8039 400	4	4	0	0	2
				CEFUROXIME AXETIL	4	4	1	0	3
				TOTAL	12	12	2	0	6

BAY 12-8039/D96-022
BRONCHITIS

APPENDIX 2 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
19	Ondrejicka	21NOV96	25OCT97	BAY 12-8039 200	7	7	3	1	4
				BAY 12-8039 400	6	6	4	3	6
				CEFUROXIME AXETIL	7	7	5	3	7
				TOTAL	20	20	12	7	17
20	Smallwood	10FEB97	26FEB97	BAY 12-8039 200	1	1	1	1	1
				BAY 12-8039 400	0	0	0	0	0
				CEFUROXIME AXETIL	2	2	1	0	2
				TOTAL	3	3	2	1	3
23	Pyke	28JAN97	29AUG97	BAY 12-8039 200	4	4	2	1	4
				BAY 12-8039 400	4	4	4	0	4
				CEFUROXIME AXETIL	3	3	3	0	3
				TOTAL	11	11	9	1	11
25	Chapman	10APR97	09NOV97	BAY 12-8039 200	1	1	1	0	1
				BAY 12-8039 400	2	2	1	0	2
				CEFUROXIME AXETIL	1	1	1	0	1
				TOTAL	4	4	3	0	4
26	Brand	12DEC96	09MAR98	BAY 12-8039 200	6	6	3	1	5
				BAY 12-8039 400	6	6	4	0	5
				CEFUROXIME AXETIL	8	8	5	1	8
				TOTAL	20	20	12	2	18
27	Felicetta	18FEB97	13MAR98	BAY 12-8039 200	5	5	4	3	5
				BAY 12-8039 400	4	4	3	1	4
				CEFUROXIME AXETIL	4	4	3	2	3
				TOTAL	13	13	10	6	12
28	Grossman.C	06FEB97	28APR98	BAY 12-8039 200	7	7	5	2	7
				BAY 12-8039 400	8	8	4	0	7
				CEFUROXIME AXETIL	6	6	4	1	6
				TOTAL	21	21	13	3	20
30	Richter	12FEB97	21OCT97	BAY 12-8039 200	2	2	1	0	2
				BAY 12-8039 400	3	3	0	0	2
				CEFUROXIME AXETIL	4	4	1	0	4
				TOTAL	9	9	2	0	8

BAY 12-8039/D96-022
BRONCHITIS

APPENDIX 2 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
31	Mullican	19DEC96	14JAN98	BAY 12-8039 200	4	4	4	0	3
				BAY 12-8039 400	4	4	1	0	3
				CEFUROXIME AXETIL	4	4	4	1	4
				TOTAL	12	12	9	1	10
32	Field	13JAN97	22JAN98	BAY 12-8039 200	2	2	2	1	2
				BAY 12-8039 400	2	2	1	1	1
				CEFUROXIME AXETIL	4	4	4	1	4
				TOTAL	8	8	7	3	7
34	Pylypchuk	03FEB97	29MAR98	BAY 12-8039 200	6	6	5	0	6
				BAY 12-8039 400	6	6	5	0	6
				CEFUROXIME AXETIL	5	5	5	1	5
				TOTAL	17	17	15	1	17
35	Grossman.R	21FEB97	01APR98	BAY 12-8039 200	4	4	4	0	4
				BAY 12-8039 400	4	4	1	0	3
				CEFUROXIME AXETIL	5	5	2	1	5
				TOTAL	13	13	7	1	12
36	Rhoades	17FEB97	17JAN98	BAY 12-8039 200	3	3	2	1	2
				BAY 12-8039 400	2	2	2	2	2
				CEFUROXIME AXETIL	3	3	2	1	2
				TOTAL	8	8	6	4	6
37	DeAbate	27MAR97	30OCT97	BAY 12-8039 200	44	44	37	36	39
				BAY 12-8039 400	44	44	40	39	42
				CEFUROXIME AXETIL	43	43	37	37	40
				TOTAL	131	131	114	112	121
38	Zorn	04APR97	12DEC97	BAY 12-8039 200	4	4	4	1	4
				BAY 12-8039 400	4	4	2	1	4
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	12	12	10	5	12
39	Gabriele	22JAN97	22JAN98	BAY 12-8039 200	2	2	2	0	2
				BAY 12-8039 400	2	2	0	0	1
				CEFUROXIME AXETIL	2	2	0	0	2
				TOTAL	6	6	2	0	5

BAY 12-8039/D96-022
BRONCHITIS

APPENDIX 2 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
43	Clark	05SEP97	16OCT97	BAY 12-8039 200	1	1	1	1	1
				BAY 12-8039 400	1	1	1	0	0
				CEFUROXIME AXETIL	1	1	1	0	1
				TOTAL	3	3	3	1	2
44	Stocks	13NOV97	07MAR98	BAY 12-8039 200	3	3	2	0	3
				BAY 12-8039 400	4	4	4	4	4
				CEFUROXIME AXETIL	4	4	4	3	4
				TOTAL	11	11	10	7	11
45	Russell	23SEP97	23APR98	BAY 12-8039 200	6	6	5	1	6
				BAY 12-8039 400	7	7	6	3	6
				CEFUROXIME AXETIL	6	6	5	5	5
				TOTAL	19	19	16	9	17
46	LaForge	05FEB98	18MAR98	BAY 12-8039 200	0	0	0	0	0
				BAY 12-8039 400	1	1	1	1	1
				CEFUROXIME AXETIL	2	2	2	2	2
				TOTAL	3	3	3	3	3
47	Kreisman	12DEC97	21DEC97	BAY 12-8039 200	0	0	0	0	0
				BAY 12-8039 400	0	0	0	0	0
				CEFUROXIME AXETIL	1	1	0	0	1
				TOTAL	1	1	0	0	1
48	Law	21OCT97	05FEB98	BAY 12-8039 200	3	3	2	1	2
				BAY 12-8039 400	3	3	3	3	3
				CEFUROXIME AXETIL	3	3	2	0	2
				TOTAL	9	9	7	4	7
49	Wainz	20JAN98	07MAY98	BAY 12-8039 200	2	2	1	0	2
				BAY 12-8039 400	2	2	2	0	2
				CEFUROXIME AXETIL	3	3	3	0	3
				TOTAL	7	7	6	0	7
50	Faris	12SEP97	06MAY98	BAY 12-8039 200	10	10	8	3	9
				BAY 12-8039 400	9	9	9	1	9
				CEFUROXIME AXETIL	10	10	10	4	10
				TOTAL	29	29	27	8	28

BAY 12-8039/D96-022
BRONCHITIS

APPENDIX 2 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
51	Markuna	22SEP97	08FEB98	BAY 12-8039 200	4	4	4	0	4
				BAY 12-8039 400	5	5	4	1	4
				CEFUROXIME AXETIL	4	4	3	0	3
				TOTAL	13	13	11	1	11
52	Safdi	09FEB98	29MAR98	BAY 12-8039 200	1	1	1	0	1
				BAY 12-8039 400	1	1	0	0	1
				CEFUROXIME AXETIL	1	1	1	0	1
				TOTAL	3	3	2	0	3
53	Jackson	07JAN98	09APR98	BAY 12-8039 200	2	2	2	1	2
				BAY 12-8039 400	2	2	1	0	2
				CEFUROXIME AXETIL	4	4	3	1	3
				TOTAL	8	8	6	2	7
54	Posner	11DEC97	09MAY98	BAY 12-8039 200	7	7	7	3	7
				BAY 12-8039 400	6	6	5	2	5
				CEFUROXIME AXETIL	7	7	4	4	4
				TOTAL	20	20	16	9	16
ALL CENTERS		18NOV96	10MAY98	BAY 12-8039 200	223	223	177	77	198
				BAY 12-8039 400	225	225	170	73	202
				CEFUROXIME AXETIL	234	234	185	85	215
				TOTAL	682	682	532	235	615

BAY 12-8039 / STUDY NUMBER 0124

APPENDIX 3

: PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP PER APPLICANT

			TREATMENT GROUP												
			BAY 12-8039 400 MG				CLARITHROMYCIN 1000 MG				NOT RANDOMIZED	ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION: MIDDLE EUROPE	AUSTRIA	95	8	8	6	1	8	7	5			16	15	11	1
		96	6	6	1	1	6	6	3	1		12	12	4	2
		ALL	14	14	7	2	14	13	8	1		28	27	15	3
	SWITZERLAND	CENTER NO.													
		194	2	2	2	2	4	4	2	1		6	6	4	3
		ALL	2	2	2	2	4	4	2	1		6	6	4	3
	FEDERAL REPUBLIC OF GERMANY	CENTER NO.													
		168	5	5	5		5	5	5			10	10	10	
		169	4	4	4	2	4	4	2	2		8	8	6	4
		170	4	4	4	1	4	4	4	2		8	8	8	3
		171	8	8	7	2	8	8	7			16	16	14	2
		172	3	3	2	1	3	3	2	1		6	6	4	2
		174	2	2	2	1	1	1	1			3	3	3	1
		176	4	4	4	2	4	4	3	2		8	8	7	4
		177	4	4	1		4	4	3	2		8	8	4	2
		178	1	1	1	1	1	1	1			2	2	2	1
		181	4	4	4	3	4	4	4	1		8	8	8	4
		183	6	6	3		6	6	6	2		12	12	9	2
		184	7	7	6	3	7	7	7	4		14	14	13	7
		185	3	3	3	2	2	2	2	2		5	5	5	4

(CONTINUED)

* SAFETY POPULATION EQUALS ITT POPULATION

APPENDIX 3 (CONTINUED)
PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP PER APPLICANT

			TREATMENT GROUP												
			BAY 12-8039 400 MG				CLARITHROMYCIN 1000 MG				NOT RANDOMIZED	ALL TREATMENT GROUPS COMBINED			
			PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION	COUNTRY	ALL													
REGION: MIDDLE EUROPE	FEDERAL REPUBLIC OF GERMANY		55	55	46	18	53	53	47	18		108	108	93	36
	NETHERLANDS	CENTER NO.													
		195	16	16	16	9	15	15	14	10		31	31	30	19
		196	4	4	3	2	4	4	4			8	8	7	2
		197	3	3	3	1	2	2	2	2		5	5	5	3
		200	2	2	2							2	2	2	
		201	7	7	6	2	7	7	5	4		14	14	11	6
		202	2	2	1	1	2	2	2	1		4	4	3	2
		ALL	34	34	31	15	30	30	27	17		64	64	58	32
	ALL		105	105	86	37	101	100	84	37		206	205	170	74
REGION: FRANCE/SOUTH EUROPE	COUNTRY	CENTER NO.													
	SPAIN	190	1	1	1	1	1	1	1			2	2	2	1
		191	1	1	1	1	1	1	1			2	2	2	1
		192	4	4	4	3	6	6	2	2		10	10	6	5
		193	3	2	2	1	4	4	4	3		7	6	6	4
		ALL	9	8	8	6	12	12	8	5		21	20	16	11
	FRANCE	CENTER NO.													
		100	2	2	2		2	2	2			4	4	4	
		101	1	1	1		2	2	2	1		3	3	3	1

(CONTINUED)

* SAFETY POPULATION EQUALS ITT POPULATION

APPENDIX 3 (CONTINUED)
PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP PER APPLICANT

			TREATMENT GROUP												
			BAY 12-8039 400 MG				CLARITHROMYCIN 1000 MG				NOT RANDOMIZED	ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID
REGION: FRANCE/SOUTH EUROPE	FRANCE	104	2	2	1		2	2	2			4	4	3	
		105	2	2	2		2	2	2	1		4	4	4	1
		106	2	2	2		2	2	2	2		4	4	4	2
		108	6	6	6		6	6	4			12	12	10	
		109	2	2	2		2	2	2			4	4	4	
		110	4	4	3		4	4	4			8	8	7	
		114	4	4	4		4	4	4	2		8	8	8	2
		116	1	1	1							1	1	1	
		117	2	2	2		2	2	2			4	4	4	
		121	4	4	4	1	4	4	2			8	8	6	1
		129	4	4	3	2	4	4	4			8	8	7	2
		135	9	9	8	3	8	8	7	2		17	17	15	5
		139	5	5	5	3	6	6	6	1		11	11	11	4
		148	1	1	1		1					2	1	1	
		151	7	7	6		8	8	7			15	15	13	
		153	2	2	1		2	2	1			4	4	2	
		155	6	6	5	2	5	5	3	1		11	11	8	3
		157	2	2	2		2	2	2			4	4	4	
		159	3	3	3	1	2	2	1	1		5	5	4	2
		161	4	4	3		2	2	2			6	6	5	

(CONTINUED)

* SAFETY POPULATION EQUALS ITT POPULATION

APPENDIX 3 (CONTINUED)
PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP PER APPLICANT

			TREATMENT GROUP												
			BAY 12-8039 400 MG				CLARITHROMYCIN 1000 MG				NOT RANDOMIZED	ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID
REGION: FRANCE/SOUTH EUROPE	FRANCE	163	4	4	4	1	4	4	4			8	8	8	1
		164	3	3	3		2	2	2	1		5	5	5	1
		166	1	1	1		1	1	1			2	2	2	
		167	1	1	1		1	1	1		1	3	2	2	
		ALL	84	84	76	13	80	79	69	12	1	165	163	145	25
	GREECE	CENTER NO.													
		186	10	10	9	3	10	10	10			20	20	19	3
		187	12	12	10	4	12	12	11	4		24	24	21	8
		189	10	10	9	4	10	10	10	5		20	20	19	9
		ALL	32	32	28	11	32	32	31	9		64	64	59	20
	ALL		125	124	112	30	124	123	108	26	1	250	247	220	56
REGION: GREAT BRITAIN	COUNTRY	CENTER NO.													
	GREAT BRITAIN (UNITED KINGDOM)	203	1	1	1	1	2	2	2			3	3	3	1
		204	4	4	4	3	3	3	2	1		7	7	6	4
		205	6	6	6	2	5	5	5	4		11	11	11	6
		206	9	9	9	1	10	10	10	1		19	19	19	2
		207	6	6	5		6	6	6	1		12	12	11	1
		208	2	2	2	2	2	2	2			4	4	4	2
		210	10	10	8	2	10	10	9	2		20	20	17	4
		211	7	7	6	2	8	8	6	4		15	15	12	6

(CONTINUED)

* SAFETY POPULATION EQUALS ITT POPULATION

APPENDIX 3 (CONTINUED)
PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP PER APPLICANT

			TREATMENT GROUP												
			BAY 12-8039 400 MG				CLARITHROMYCIN 1000 MG				NOT RANDOMIZED	ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID	PATIENTS ENROLLED	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICRO BIOL. VALID
REGION: GREAT BRITAIN	GREAT BRITAIN (UNITED KINGDOM)	212					2	2	2			2	2	2	
		214	5	4	3	1	6	6	4	1		11	10	7	2
		215	6	6	5	1	6	6	5	1		12	12	10	2
		216	6	6	6	3	5	5	5	1		11	11	11	4
		219	2	2	2	1	2	2	2	2		4	4	4	3
		220	6	6	5	3	6	6	6	4		12	12	11	7
		221	1	1	1	1	1	1	1	1		2	2	2	2
		222	8	8	7	1	8	8	7	5		16	16	14	6
		223	6	6	5	3	6	6	5	2		12	12	10	5
		224	2	2	2							2	2	2	
		225	11	11	8	4	10	10	10	4		21	21	18	8
		226	4	4	3		4	4	2			8	8	5	
		227	2	2	1	1	2	2	2	1		4	4	3	2
		228	2	2	1		2	2	2	1		4	4	3	1
		229	1	1	1	1	1	1	1	1		2	2	2	2
		230	7	7	5	3	8	8	8	2		15	15	13	5
		232	9	9	7	3	9	9	8	2		18	18	15	5
		233	2	2	2	1	3	3	3			5	5	5	1
		234	3	3	2		3	3	3	1		6	6	5	1
		236	2	2	1		2	2	2	2		4	4	3	2

(CONTINUED)

* SAFETY POPULATION EQUALS ITT POPULATION

APPENDIX 3 (CONTINUED)
PATIENT ENROLLMENT BY COUNTRY, INVESTIGATOR AND TREATMENT GROUP PER APPLICANT

			TREATMENT GROUP												
			BAY 12-8039 400 MG				CLARITHROMYCIN 1000 MG				NOT RANDOMIZED	ALL TREATMENT GROUPS COMBINED			
REGION	COUNTRY	CENTER NO.	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID	PATIENTS ENROLLED	PATIENTS ENROLLED	VALID FOR ITT *	VALID PER PROTOCOL	MICROBIOL. VALID
REGION: GREAT BRITAIN	GREAT BRITAIN (UNITED KINGDOM)	238	14	14	14	7	14	14	14	7		28	28	28	14
		239	2	2	2	1	2	2	1			4	4	3	1
		ALL	146	145	124	48	148	148	135	51		294	293	259	99
	ALL		146	145	124	48	148	148	135	51		294	293	259	99
ALL			376	374	322	115	373	371	327	114	1	750	745	649	229

MEDICAL OFFICER'S REVIEW OF NDA

NDA 21-085
AVELOX

Applicant
Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, Connecticut 06516
Contact: Mr Andrew Verderame, Associate Director, Regulatory Affairs
Phone: 203-812-5172

Submission/Review Dates

Date of submission:	December 9, 1998
Date received by CDER:	December 10, 1998
Date review started:	January 11, 1999
Date review completed:	November 15, 1999

Drug Identification

Generic name:	moxifloxacin (BAY 12-8039)
Proposed trade name:	Avelox
Pharmacologic category:	antimicrobial-fluoroquinolone
Dosage formulation:	400 mg tablet
Route of administration:	oral

Regulatory materials reviewed
NDA 21-085, volumes 1.1-1.2, 1.269-1.298 and associated electronic files, submitted 12/9/98

[redacted]

NDA 20-596 (Raxar), MO review
NDA 20-677 (Zagam), MO review

Regulatory Background
PreNDA meeting: February 13, 1998
Advisory Committee meeting: October 21, 1998

CLINICAL STUDIES
Introduction

This application included data from clinical studies to support [redacted] indications, acute sinusitis, acute bacterial exacerbation of chronic bronchitis (ABECB), [redacted] community acquired pneumonia (CAP). The CAP indication is reviewed below. The reader is referred to the following documents for the remaining sections of the review of clinical data: 1) acute sinusitis - MO review of Dr Eric Mann, 2) ABECB- MO review of Dr John Powers, [redacted] MO review of Integrated Summary of Safety, Dr Leonard Sacks.

INDICATION: COMMUNITY- ACQUIRED PNEUMONIA
Introduction

Pneumonia, together with influenza, is the sixth leading cause of death in the United States; there are an estimated 4 million cases annually (10). Fifty to 80% of these patients are managed in an ambulatory setting (11). A discussion of the etiologic agents of this infection should recognize 1) that most of the data for the microbial etiology of CAP comes from studies of in-patients, 2) that the predominant organisms infecting out-patients with community-acquired pneumonia may differ from those infecting in-patients, and 3) that the organisms that cause CAP in out-patients probably represent a mixture of agents some of which require antimicrobial therapy, others of which cause self-limited disease.

In the preantibiotic era, bacteremic lobar pneumonia occurred in 1 of 100 persons in the US population per year. It was caused by *S. pneumoniae* in 95% of cases. The incidence of bacteremic pneumococcal pneumonia in recent years is one-tenth to one-one hundredth that number (13). Since the onset of the antibiotic era, *S. pneumoniae* has remained important as the single most commonly defined pathogen in hospitalized patients with CAP (2). Though hospitalized patients are the source of the most reliable diagnostic information such as blood and empyema cultures, individuals with community-acquired pneumonia are, for the large part, managed as out-patients. Based on the estimates provided above, between 2 and 3 million CAP patients per year in the US are managed as out-patients.

Perhaps more severe (ie. those requiring hospitalization) cases of CAP are associated with a different group of organisms than less severe cases (ie. those that can be managed as out-patients). This principle has been readily accepted when considering etiologic agents of CAP necessitating admission to the ICU, as evidenced by various management guidelines published in recent years (1, 3). A small number of studies of ambulatory CAP attest to a possible difference in etiologic agents in this subpopulation that is the large majority of those patients with community-acquired pneumonia. These studies are discussed below.

In 1998, Marrie elaborated on this distinction between out-patients and in-patients in the consideration of the etiology of CAP. Table 1, taken from reference 11 and presented below, summarizes the data used by Marrie to conclude that 1) *M. pneumoniae* is more

common in ambulatory patients than those requiring admission to the hospital and 2) the importance of bacterial pathogens is underestimated in these studies because many out-patients do not have sputum specimens collected. Also noteworthy in Table 1 is the repeated finding that ~50% of patients with CAP who are managed as out-patients do not have an etiologic agent identified.

Table 1. Etiology of CAP treated on an ambulatory basis (from Marrie, 1998)

Author	Location	Date	# pts	*S. pneum*	*H. influ*	*M. pneum*	*C. pneum*	Unknown cause
Berntsson et al, 1986	Sweden	3 yr period	54	5 (9%)	6 (12 %)	20 (37%)	ND	41%
Marrie et al, 1996	Nova Scotia	1991-94	149	1	1	34 (22.8%)	16 (10.7%)	48%
Erard et al, 1991	Switz-erland	4 yr	161*	17 (11%)	3 (2%)	22 (17.4%)	ND	47%
Langille et al, 1993	Nova Scotia	1989-90	75**	-	-	22 (29%)	1/19 (5.3%)	55%
TOTAL			439	23 (5%)	10 (2.3 %)	104 (24%)		211 (48%)

*8.7% required hospitalization
** 35% required hospitalization

BAY 12-8039 (moxifloxacin) is a fluoroquinolone developed by Bayer AG which appears to expand on the antimicrobial spectrum of activity of older fluoroquinolones, the prototype of which is ciprofloxacin, also a Bayer product. [redacted] for the study of the oral formulation of this drug, was submitted in December 1995. [redacted] for the study of the intravenous formulation, was submitted in February 1997. BAY 12-8039 is thought to have gram negative activity comparable to that of ciprofloxacin except that it is not as active against *Pseudomonas aeruginosa*. It is also thought to have markedly improved *in vitro* activity against gram positive organisms when compared with older fluoroquinolones. The sponsor has shown data suggesting that 12-8039 has an eightfold increase in activity against *Streptococcus pneumoniae* when compared with ciprofloxacin (MIC_{90} 0.25 ug/ml v. 2.0 ug/ml) and a tenfold increase in activity against methicillin-susceptible *S. aureus* (MSSA) when compared with ciprofloxacin (MIC_{90} BAY 12-8039 0.062 ug/ml).

In the last decade, development of drugs with activity against *S. pneumoniae* has assumed increasing importance because of the recognition of rising rates of pneumococcal resistance to penicillin and to other drugs traditionally relied upon to treat infections caused by this common and virulent organism. BAY 12-8039 has been developed coincident with this recognition, and the sponsor has presented *in vitro* data supporting activity of this drug against penicillin-susceptible and penicillin-resistant strains of *S.*

pneumoniae. The sponsor has also provided data suggesting good activity against pathogens of atypical pneumonia such as *Mycoplasma*, *Legionella*, and *Chlamydia* species.

NDA 21-085 included data from five clinical trials to support the indication of community-acquired pneumonia (CAP). There were three controlled phase III trials; study #D96-026 was conducted in the United States and studies #0140 and #0119 were conducted outside the US. There was one uncontrolled phase III trial; study #D96-025 was conducted in the US. There was one phase II trial; study #0112 was conducted in South Africa. Following the **Draft labeling excerpt**, each of these five studies is reviewed separately below.

Draft labeling excerpt
From the INDICATIONS AND USAGE section:

Avelox Tablets are indicated for the treatment of adults (≥ 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* [redacted] *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, or *Moraxella catarrhalis*.

> MO COMMENT: The draft labeling for a second indication, acute maxillary sinusitis, also includes a claim for clinical efficacy in the treatment of this infection caused by strains of *S. pneumoniae* that are penicillin-susceptible, intermediate, and resistant.

From the DOSAGE AND ADMINISTRATION section:

The [redacted] dose of Avelox tablets is one 400 mg tablet taken orally every 24 hours. The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	[redacted] Duration
Community Acquired Pneumonia	400 mg	10 days

STUDY NO. D96-026

Prospective, randomized, double-blind multi-center comparison of the safety and efficacy of moxifloxacin 400 mg QD for 10 days versus clarithromycin 500 mg BID for the treatment of patients with community acquired pneumonia

STUDY DESIGN

This equivalence study was conducted at 61 centers in the United States from November 1996 to June 1998. Moxifloxacin was compared in a 1:1 randomization to an approved comparator, clarithromycin, for both efficacy and safety in the treatment of CAP. The approved dose of clarithromycin [redacted] for the treatment of CAP due to *S. pneumoniae, M. catarrhalis,* and *C. pneumoniae* is 250 mg bid for 7 to 14 days. In the final study report for D96-026, the applicant noted this approved dose for clarithromycin for CAP and also noted that the approved dose for ABECB due to *H. influenzae* is 500 mg bid. The applicant explained that clarithromycin 500 mg bid was chosen as the comparator agent for the study under review in order to provide enhanced coverage for *H. influenzae*, an important pathogen in smokers with CAP.

> MO COMMENT: The applicant selected a higher dose than that approved for clarithromycin for the treatment of CAP. This dose of the comparator agent provides a more stringent assessment of moxifloxacin efficacy for this indication caused by the organisms listed above. It should also be noted that [redacted] is not approved for CAP due to *H. influenzae,* and therefore may not be the best comparator for the purpose of assessing moxifloxacin efficacy in infections caused by this agent. The use of this higher dose of clarithromycin for CAP cannot be used to substantiate any potential claims of an enhanced safety profile for moxifloxacin compared with clarithromycin.

Patients aged 18 years or older with signs and symptoms consistent with bacterial pneumonia were eligible for enrollment. Evidence of CAP was to be documented by the presence of all three of the following criteria:

- Fever and/or leukocytosis
- One or more of the following: productive cough, purulent sputum, dyspnea or tachypnea, rigors/chills, pleuritic chest pain, rales/rhonchi and/or evidence of pulmonary consolidation
- Radiological evidence of a new or progressive infiltrate consistent with community acquired pneumonia.

A protocol amendment (#4, dated 3/31/98) was implemented before completion of the study to allow inclusion of patients who had CAP but did not have fever and/or leukocytosis. This amendment modified the inclusion criteria such that patients who met both of the following modified criteria could be evaluable for efficacy:

- Two or more of the following: fever and/or leukocytosis, productive cough, purulent sputum, dyspnea or tachypnea, rigors/chills, pleuritic chest pain, rales/rhonchi and/or evidence of pulmonary consolidation

- Radiological evidence of a new or progressive infiltrate consistent with community acquired pneumonia.

This modification was made following discussion with the review division, when it was also established that, because of the pivotal role of radiologic findings in these modified criteria, radiologists' chest x-ray reports be available to confirm the diagnosis of CAP. The final study report stated that chest x-rays were read by either the clinical investigator or a radiologist. Thus a radiologist's report was not available for all chest x-rays, but all available x-ray reports, whether read by clinician or radiologist, were collected and filed at Bayer.

> MO COMMENT: If the evaluability of an individual patient is questionable, the x-ray report can sometimes be helpful in resolving this issue. Patients for whom there is a question of evaluability for whom no x-ray report available may be considered unevaluable.

Exclusion criteria of note were patients with severe cardiac failure (NYHA Class IV), patients with severe respiratory tract infections requiring parenteral therapy or mechanical ventilatory support, patients with suspected aspiration pneumonia, patients hospitalized more than 48 hours, patients with significant liver impairment (SGOT, SGPT, and/or total bilirubin >3x upper limit of normal), patients with significant renal impairment (Cr >3.0 mg/dl or Cr clearance <30 cc/min), and patients with coexistent disease thought likely to affect the outcome of the study, including lung cancer, lung abscess, connective tissue disease affecting the lungs, empyema. A protocol amendment (#3, dated 5/27/97) also excluded patients with prolonged QT interval on EKG or patients taking medication reported to increase the QT interval.

> MO COMMENT: The draft label submitted by the applicant does not distinguish among degrees of severity of CAP. The exclusion of patients with severe CAP in the study under review suggests that all CAP studies in NDA 21-085 be reviewed for such an exclusion. If patients with severe CAP were systematically excluded, the INDICATIONS AND USAGE section of the label should be modified to reflect the mild to moderate illness of the CAP population studied.

In addition to the clinical and radiologic evaluations described above, certain laboratory tests were performed prior to enrollment. These included sputum gram stain and bacterial

culture, serology for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections, throat and nasopharyngeal swabs for *Mycoplasma* and *Chlamydia* cultures (and in the case of *Mycoplasma*, throat swab for PCR also), sputum for *Mycoplasma* culture and PCR, and *Legionella pneumophila* culture, and urine for *Legionella* antigen assay. Routine hematology (complete blood count or CBC) serum chemistries, and urinalysis were also performed.

Once randomized and started on treatment, patients were instructed to return on Day 3-5 of treatment (During Therapy Visit), Day 2-4 post-treatment (End of Therapy Visit or EOT), and Day 21-28 post-treatment (Follow-up Visit or F/U). Clinical, laboratory, and compliance assessments were made at these visits.

The applicant first determined that the primary efficacy endpoint for this study was to be clinical response at end of therapy (EOT). During the conduct of the study, draft FDA guidelines were released which specified that the primary time point for evaluating efficacy should be at least 5 elimination half-lives of the study drug or 7 days after the end of treatment, whichever was longer. A protocol amendment (#2, dated 3/25/97), was implemented to change the primary efficacy endpoint to clinical response at follow-up (F/U), 21-28 days following the completion of therapy. Prior to unblinding, the window for this F/U visit was expanded to 14-35 days following the completion of therapy in order to maximize the number of evaluable patients. This modification was made following discussion with the review division, when it was also established that any failures at EOT would be 'carried forward' and included in the population of overall failures.

Patients were considered evaluable or valid for efficacy analysis if they met the clinical criteria for the diagnosis of CAP as noted above, if no other systemic antibacterial agents were administered concomitantly with the study drug, if study drug were given for a minimum of 48 hours if the result of therapy were a failure, or a minimum of 5 days if the result were a success, if compliance with dosing were $\geq$ 80%, if there were no protocol violations which influenced treatment efficacy, if the random code were not broken, if there were no missing or 'indeterminate' essential data which could not be recovered.

> MO COMMENT: The applicant described the primary efficacy endpoint for this study as clinical outcome at the F/U visit in a clinically evaluable patient population. This is consistent with FDA guidelines for CAP studies set forth in both the 1992 Points to Consider Document and the 1997 Draft Guidance for Industry.
>
> MO COMMENT: The MO also analyzed efficacy by evaluating the clinical outcome of the clinically evaluable population at the F/U visit. For a more detailed description of the MO analysis, the reader is referred to the STUDY RESULTS section, 'Evaluability and efficacy, MO assessment' subsection. For a discussion of the intent to treat analysis, the reader is referred to the Biostatistics Review.

MO COMMENT: Assessments of clinical efficacy included 'resolution' or 'failure or relapse' at both EOT and F/U visits. The applicant also calculated 'overall' success or failure by carrying forward any failures at EOT and including them in the outcome assessment at F/U. The MO analysis assessed overall success or failure at F/U.

The applicant also performed a second efficacy analysis of patients who were both clinically and microbiologically evaluable. Clinical response and bacteriologic eradication rates were evaluated for this population.

MO COMMENT: The MO analysis of patients who were clinically and microbiologically evaluable assessed clinical response in patients for whom a microbiologic etiology of CAP could be established using results of sputum gram stain, sputum culture, serology, and/or sputum or mucosal swab PCR.

STUDY RESULTS

Demographics

There were 474 patients enrolled in this study; 237 were treated with BAY 12-8039 and 237 with clarithromycin. Demographic characteristics of patients in both treatment arms are presented in Table 2. The groups were well matched for gender, race, age, weight, and smoking history.

Table 2. Demographic variables by treatment group

	BAY 12-8039	Clarithromycin
Sex, % female	54%	51%
Race, % caucasian	79%	83%
Age at Enrollment (Yrs), Mean	48	49
Weight (kg), Mean	80	78
Cigarette smoker	63%	61%
Mean # cigarettes smoked/day	20	22
Mean years of smoking	25	25

Evaluability and efficacy

Clinically evaluable population

Applicant assessment

Table 3 presents the applicant's analysis of clinical outcome in those patients who were clinically evaluable for efficacy analysis. As noted above, inclusion in this study population did not require that a microbiologic etiology of the patient's infection be identified.

Table 3. Clinical response in clinically evaluable population- applicant assessment

	BAY 12-8039	Clarithromycin
End of Therapy		
Resolution	177/183 (96.7%)	173/182 (95.0%)
Failure or Relapse	6/183 (3.3%)	9/182 (5.0%)
Follow-up		
Resolution	184/188 (97.9%)	178/179 (99.4%)
Failure or Relapse	4/188 (2.1%)	1/179 (0.6%)
Overall* Success	184/194 (94.8%)	178/188 (94.7%)
Failure	10/194 (5.2%)	10/188 (5.3%)
* 95% Mantel-Haenszel Confidence Interval for Difference in Rates Controlling for Center (BAY 12-8039 - Clarithromycin)	(-3.7%, 5.3%)	
95% Confidence Interval for Difference in Rates (BAY 12-8039 - Clarithromycin) using Yates' Continuity Correction	(-4.8%, 5.2%)	

Clinically evaluable population
MO assessment

Evaluability and efficacy in the clinically evaluable population were assessed by the MO using a sampling technique. A random sample of 20% of the study population was generated. Individual CRTs and pertinent databases for each of these patients were reviewed by the MO for agreement between the MO and applicant regarding evaluability and outcome. The MO assessed patient evaluability with the following scheme:

> Because the inclusion criteria had been amended to include patients who did not present with fever or leukocytosis, the importance of the radiologic finding of a pulmonary infiltrate was considered paramount. Thus patients in the sample were first reviewed to verify the presence of an infiltrate at enrollment and exclude other underlying pulmonary parenchymal disease such as tumor or abscess. Vital signs were next reviewed for the presence or absence of fever. In patients who were afebrile, the MO accepted tachypnea or expanded the inclusion criteria to include tachycardia as a clinical finding consistent with CAP. The database of signs and symptoms was next reviewed for findings consistent with pneumonia for patients who had normal vital signs at enrollment. Greatest weight was given to the findings of cough, pleuritic chest pain, and rigors. For patients with normal vital signs whose clinical findings were not strongly suggestive of CAP (ie rhonchi, mild chills) the database for sputum characteristics was also reviewed,

with additional consideration for evaluability given to patients with purulent or blood-tinged sputum. Next, evaluability of patients in the sample was assessed by reviewing the database of concomitant medications for patients who received antimicrobial agents other than study drug during the treatment or follow-up periods. Lastly, the sample population was reviewed for the date of the test-of-cure (TOC) visit. Any patients whose TOC visit was ≥ 7 days following the end of therapy was considered evaluable by the MO.

The MO assessed then patient outcome with the following scheme:

> The database listing all patients who were hospitalized during the study was first reviewed to establish that the outcome at the end of study determined by the applicant was consistent with the need for hospitalization during the study. Then vital signs and signs and symptoms were reviewed for each patient to assess clinical course throughout the course of the study. The database that included investigator comments was also reviewed to resolve any questions regarding patient evaluability or outcome.

Review of the sample as described above resulted in the reclassification of two patients in each treatment group by the MO. All four of these patients were considered evaluable and cured by the applicant's analysis. The MO reclassified each of these patients as unevaluable. Analysis of these reclassifications with the Biostatistics reviewer demonstrated adequate agreement with the applicant's findings such that the MO accepted the applicant's assessment of the primary efficacy endpoint, evaluability and clinical outcome of the clinically evaluable population at the TOC visit. These data, presented above in Table 3, demonstrate a high efficacy rate for moxifloxacin in the treatment of CAP that is shown to be statistically equivalent to that of an approved comparator, clarithromycin. The lower bound of 95% CI around the difference in point estimates of efficacy rates if >-10%. As noted above, the dose of clarithromycin used in the study under review (500 mg bid x 10 days) was twice that of the approved dose for community acquired pneumonia due to *S. pneumoniae, M. catarrhalis,* and *C. pneumoniae* (250 mg bid x 7-14 days).

Microbiologically and clinically evaluable population
Applicant assessment

Table 4 presents the applicant's assessment of clinical efficacy in microbiologically and clinically evaluable patients by infecting organism.

Table 4. **Clinical Resolution Rates of Proposed Dosing Regimen at the Test-of-Cure Visit (F/U) by Organism**

	BAY 12-8039 400 mg q D	Clarithromycin 500 bid
Streptococcus pneumoniae	17/17 (100%)	18/19 (95%)
Haemophilus influenzae	22/23 (96%)	16/16 (100%)
Mycoplasma pneumoniae	23/24 (96%)	20/20 (100%)
Chlamydia pneumoniae	48/51 (94%)	48/49 (98%)
Staphylococcus aureus	5/5 (100%)	5/5 (100%)
Moraxella catarrhalis	6/7 (86%)	2/2 (100%)
Klebsiella pneumoniae	6/6 (100%)	5/5 (100%)

MO assessment

The MO analysis of clinical efficacy in microbiologically and clinically evaluable patients was organized around the following three issues:

1. The draft label submitted by the applicant states that moxifloxacin is indicated for treatment of pneumococcal pneumonia due to penicillin-susceptible, intermediately susceptible, and resistant strains of *S. pneumoniae*. To date, no antimicrobial agent has a labeled indication for treatment of any infection caused by penicillin-resistant *S. pneumoniae*. The demonstration of such efficacy has met with a number of difficulties that were raised and discussed at two public meetings involving FDA and representatives of the pharmaceutical industry. The first of these was a workshop with industry in July 1998, the second an Advisory Committee meeting in October 1998.

   Following discussion at these meetings, a consensus was reached that a number of different types of data could be supportive of a claim of clinical efficacy in the treatment of an infection due to a resistant pathogen. These types of data included *in vitro* testing, animal models of disease, pharmacokinetic studies, pharmacokinetic/pharmacodynamic models, and clinical studies of patients infected with resistant and with susceptible strains of the organism in question. Indeed, activity against susceptible strains of the organism of interest was viewed as particularly helpful in the evaluation of a drug when clinical isolates of resistant strains were scarce.

   Preclinical data were not consistently supportive of clinical efficacy of BAY 12-8039 against *S. pneumoniae*. As noted above, MIC values and data from animal models of pneumococcal disease supported the antipneumococcal activity of moxifloxacin. However pharmacodynamic models, specifically values of AUC/MIC for both the 200 mg and 400 mg doses, were both on the low side for moxifloxacin/ *S. pneumoniae*. As was noted repeatedly in the public meetings mentioned above, clinical isolates of *S. pneumoniae* that are resistant to penicillin (MIC $>$ 2.0 µg/ml) have not been readily isolated from clinical specimens.

   In general, quinolone activity against gram-positive organisms has been highly variable in the first decade of use of this class of agents. When these drugs were first used in the mid -1980s, early quinolones such as ciprofloxacin were noted to have

excellent *in vitro* activity against *S. aureus*. Resistance of *S. aureus* strains was observed to develop so quickly, that by the mid- 1990s, ciprofloxacin was not clinically useful in the treatment of staphylococcal infections. Breakthrough pneumococcal bacteremia in patients with respiratory infections treated with fluoroquinolones also called into question the utility of these agents in the treatment of gram- positive infections. In the last 3 years, newer quinolones with markedly improved *in vitro* activity against gram-positive organisms have been approved for marketing in the US. As a class, these agents have promise, but have yet to demonstrate durability in the treatment of any gram-positive infections. Indeed, a recent Canadian survey of drug susceptibility testing of over 7000 pneumococcal isolates suggested that the prevalence of pneumococci with reduced susceptibility to fluoroquinolones was increasing in Canada. This has been observed to correlate with increased use of drugs of this class (Chen et al 1999; NEJM 341:233-9). The relatively brief period of clinical experience of newer fluoroquinolones in the treatment of gram-positive infections and the paucity of clinical isolates that are resistant to penicillin in NDA 21-085 make the demonstration of clinical efficacy of moxifloxacin in CAP caused by penicillin-susceptible isolates of *S. pneumoniae* central to the review of this indication.

On 8/23/99, the MO requested that the applicant provide a list of those patients in study # D96026 who were considered to have CAP caused by *S. pneumoniae*. On 8/27/99 the applicant provided line listings for 36 patients including characterization of the isolate as susceptible (S), intermediate (I), or resistant (R) according to the breakpoints described above, clinical outcome, and microbiologic outcome. After review of the microbiologic databases submitted with the original NDA, the MO determined that there were no additional patients infected with *S. pneumoniae* who were evaluable for clinical outcome. The MO reviewed the microbiologic and clinical data for all of these 36 patients. Microbiologic data were verified by reviewing three different databases submitted with the original NDA. In two of these databases, species name and MIC values for both penicillin and BAY 12-8039 were provided. In the third, all organisms isolated from the patient were listed by visit, no MIC data were provided. The MO review was restricted to those isolates from the pretreatment visit. There were two purposes to this review of microbiologic data. The first was to assess clinical efficacy in patients infected with penicillin-susceptible *S. pneumoniae* in both treatment groups; the second was to verify the number of isolates that were I or R to penicillin and assess clinical efficacy in patients infected with these penicillin non-susceptible isolates. There was some discordance between the applicant and MO assessments of infecting organism.

Of the 36 patients considered to be infected with *S. pneumoniae*, the applicant listed 29 as the source of isolates that were susceptible or indeterminate penicillin susceptibility, 3 as intermediate, and 4 as resistant to penicillin. The MO found that there were 30 patients that were the source of isolates susceptible to penicillin or indeterminate, 3 that were intermediate, 2 that were resistant to penicillin, and one patient in whom pneumococcal infection could not be verified. Of the 36 patients listed by the applicant, 17 received treatment with moxifloxacin. There was one

patient (no. 798) who was considered a clinical failure. That patient received clarithromycin. The MO also reviewed the database documenting hospitalizations; no patients in either treatment group was hospitalized for clinical deterioration during the study. According to either applicant or MO assessment of evaluability, efficacy of moxifloxacin in the treatment of CAP due to *S. pneumoniae* that is susceptible to penicillin was shown to be 100% (17/17 or 12/12, respectively). Table 5 below presents applicant and MO assessments of evaluability of patients infected with *S. pneumoniae*. Table 6 presents applicant and MO assessments of outcome in this same population.

Table 5. Evaluability of patients infected with *S. pneumoniae*- MO reclassifications

Reason	N and Patient #
MO unable to verify MIC data APPL classified I, MO indeterminate* APPL classified R, MO indeterminate*	N=3 Patient #s 133, 241 Patient # 507
MO assessment of MIC different APPL classified R, MO I APPL classified S, MO I	N= 2 Patient #577, MIC to PCN 0.125 µg/ml Patient # 193, MIC to PCN 1.0 µg/ml
MO unable to verify *S. pn* infection	N=1, Patient #599, isolate nonviable

S= susceptible, I=intermediate, R=resistant

* Indeterminate = *S. pn* isolated but MIC not verified by MO search of three microbiology databases in NDA

Table 6. Clinical efficacy in patients infected with *S. pneumoniae*- Applicant and MO

Penicillin susceptibility of *S. pneumoniae* isolate	Clinical efficacy - Applicant		Clinical efficacy - MO	
	Moxifloxacin	Clarithromycin	Moxifloxacin	Clarithromycin
S or indeterminate	17/17 (100%)	18/19 (94.7%)	12/12 (100%)	18/19 (94.7%)
I (MIC > 0.1, ≤ 2.0 µg/ml)	1/1 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
R (MIC > 2.0 µg/ml)	3/3 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)

Table 6 demonstrates high clinical efficacy rates for moxifloxacin in the treatment of CAP due to *S. pneumoniae* that is susceptible or of indeterminate susceptibility to penicillin. Efficacy rates, as determined by applicant or MO, are equivalent to clarithromycin used at a dose that is higher than that in the approved label. Table 6 suggests efficacy in CAP due to pneumococcal isolates that are of intermediate susceptibility or resistant to penicillin. MO reclassification of patients as shown in Table 5 did not effect the calculation of efficacy rates, but resulted in smaller numbers of patients with susceptible or frankly resistant isolates.

An additional analysis by the MO of failures in study #D96026 suggested that patients infected with *S. pneumoniae* were not over-represented among the failures when compared with the proportion of the total study population as determined by the

applicant. These data are presented below in Table 7. As noted above, there has been a high degree of agreement between the applicant and MO assessments of clinical outcome.

Table 7. Microbiologic etiologies of clinical failures- MO assessment

Etiologic agent (s)	% of all Failures	% of total study population
S. pneumoniae	5% (1/20)	7.5% (36/474)
H. influenzae	5% (1/20)	8.2% (39/474)
M. catarrhalis	5% (1/20)	1.8% (9/474)
Mycoplasma or *Chlamydia*	80% (16/20)	30.3% (144/474)
Not determined	5% (1/20)	47.4% (225/474)

2. The draft label submitted by the applicant states that moxifloxacin is indicated in the treatment of CAP caused by two atypical pathogens, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. As presented in Table 1, Marrie noted that about 25% of out-patients with CAP had evidence of *M. pneumoniae* infection, between 5-10% had evidence of *C. pneumoniae* infection, and approximately 50% had CAP of an unknown cause. As noted in Table 4, the applicant found that 144 patients had evidence of infection with one of these two atypical agents; this represents 30% (144/474) of the total study population. The applicant also found that 47% (225/474) were not microbiologically evaluable (ie. did not have a microbiologic etiology identified). Such findings can be considered consistent with Marrie's previously published data. Because the proportion of patients with evidence of infection due to *M. pneumoniae* and *C. pneumoniae* are comparable to observations made in previously published series, and because there was a high level of accord between MO and applicant assessments of outcome, there is evidence that moxifloxacin is efficacious in the treatment of CAP due to these two organisms.

3. The draft label submitted by the applicant states that moxifloxacin is indicated in the treatment of CAP due to *S. aureus* and *K. pneumoniae*. Both of these agents cause a serious illness that is unlikely to be managed in an ambulatory patient. The epidemiology of *S. aureus* pneumonia suggests that this devastating infection is most likely to affect young infants and the elderly, particularly in the setting of an influenza outbreak. It is also associated with bronchiectasis and with post-obstructive pneumonia in patients with lung cancer; these two populations were specifically excluded from this study. CAP due to *K. pneumoniae* is a severe necrotizing infection which, when community-acquired, is associated with alcoholism and/or aspiration. Patients with underlying liver disease and those with a likelihood of aspiration pneumonia were specifically excluded from this study. Marrie's data on ambulatory CAP suggest that bacterial etiologies are under-recognized in out-patients because sputum examinations are so rarely undertaken in this population. However he reported that even in hospitalized patients, *S. aureus* accounts for about 3% of cases and all aerobic gram-negative rods for about 4% of cases (Marrie, IDCNA 1998). The severity of pulmonary infections caused by these two agents and the low frequency

with which they are shown to cause CAP even in hospitalized patients makes it highly unlikely that these organisms would be etiologic agents in the ambulatory patients enrolled in study #D96026. The MO did review all microbiologic and clinical data on all patients reported to be infected with these agents. The majority of these patients were considered by the applicant to be co-infected with two or more organisms. None of these patients had a severe enough illness and adequate microbiologic data to be considered infected with *S. aureus* or *K. pneumoniae.*

SAFETY

Extent of exposure

Of the 474 patients enrolled in the study, 473 were evaluable for safety. One patient who was randomized to clarithromycin did not return for follow-up and did not report any adverse events, thus was excluded from the safety analysis. The entire course of study drug therapy was completed by 89% of the patients who received moxifloxacin and by 85% of the patients who received clarithromycin.

Adverse events

Table 8 compares various adverse event rates between the BAY 12-8039 and clarithromycin treatment groups. These rates were similar for each group. It should be noted that the dose of clarithromycin used in the study under review was twice the labeled dose for community-acquired pneumonia.

Table 8. Summary of adverse events

	BAY 12-8039 400 mg (N=237)	Clarithromycin (N=236)
Any Adverse Event	117 (49%)	118 (50%)
Any Drug-Related Event	84 (35%)	81 (34%)
Any Serious Event	9 (4%)	14 (6%)
Discontinued due to AE	6 (3%)	12 (5%)
Died	1 (<1%)	1 (<1%)

Adverse event rates that occurred in at least 2% of either treatment group are presented in Table 9, and treatment-related adverse event rates that occurred in at least 2% of either treatment group are presented in Table 10.

Table 9. Incidence of adverse events occurring in at least 2% of any treatment group

Adverse Event	BAY 12-8039 400 mg (N=237)	Clarithromycin (N=236)
Any event	117 (49%)	118 (50%)
Headache	16 (7%)	15 (6%)
Abdominal pain	8 (3%)	5 (2%)
Back pain	7 (3%)	4 (2%)
Asthenia	7 (3%)	5 (2%)
Chest pain	4 (2%)	8 (3%)
Nausea	22 (9%)	21 (9%)
Diarrhea	20 (8%)	29 (12%)
Vomiting	13 (5%)	11 (5%)
Dyspepsia	6 (3%)	6 (3%)
Constipation	5 (2%)	4 (2%)
Anemia	4 (2%)	0 (0%)
Dizziness	11 (5%)	8 (3%)
Insomnia	9 (4%)	10 (4%)
Asthma	6 (3%)	3 (1%)
Rhinitis	6 (3%)	4 (2%)
Dyspnea	4 (2%)	5 (2%)
Lung disorder	1 (<1%)	4 (2%)
Rash	5 (2%)	5 (2%)
Pruritus	0 (0%)	4 (2%)
Taste perversion	10 (4%)	17 (7%)
Vaginal moniliasis	4 (2%)	1 (<1%)

Table 10. Incidence of treatment-related adverse events occurring in at least 2% of any treatment group

Adverse Event	BAY 12-8039 400 mg (N=237)	Clarithromycin (N=236)
Any event	84 (35%)	81 (34%)
Abdominal pain	6 (3%)	4 (2%)
Headache	6 (3%)	11 (5%)
Asthenia	4 (2%)	2 (<1%)
Nausea	21 (9%)	19 (8%)
Diarrhea	19 (8%)	22 (9%)
Vomiting	11 (5%)	7 (3%)
Constipation	4 (2%)	2 (<1%)
Dyspepsia	4 (2%)	3 (1%)
Dizziness	10 (4%)	6 (3%)
Insomnia	3 (1%)	6 (3%)
Rash	4 (2%)	3 (1%)
Taste perversion	10 (4%)	16 (7%)

MO COMMENT: The MO reviewed the complete line listings for all adverse events and all treatment-related adverse events. In those listings, there were no additional adverse events that were clinically noteworthy.

The most common drug-related adverse events in the BAY 12-8039 group were nausea (9%), diarrhea (8%), and vomiting (5%). Dizziness (4%) and taste perversion (4%) were also seen with relatively high frequency in this group. The most common drug-related adverse events in the clarithromycin group were diarrhea (9%), nausea (8%), and taste perversion (7%). Headache (5%) was also seen with relatively high frequency in this group.

MO COMMENT: When incidence rates were considered, BAY 12-8039 400 mg per day had a safety profile for gastrointestinal adverse events similar that of clarithromycin 500 mg per day.

Deaths and serious adverse events
There were two deaths during the monitoring period of the study. Patient 631, who received BAY 12-8039, died of a Fiorinal overdose 13 days after completing study drug therapy. Patient 958, who received clarithromycin, died from a brain tumor 25 days after the end of study drug therapy. Neither of these deaths was related to study drug.

MO COMMENT: The MO reviewed the narratives of each of the above patients' courses and concurs with the above conclusions.

A total of 18 patients were prematurely discontinued from study drug therapy due to adverse events, 6 in the BAY 12-8039 treatment group and 12 in the clarithromycin treatment group. Discontinuations due to nausea and/or vomiting were much more frequent in the clarithromycin group (6 of 12) than in the BAY 12-8039 group (one of 6). Four of the 6 patients in the BAY 12-8039 treatment group discontinued for reasons including digestive events (2 diarrhea, 1 vomiting, 1 abdominal pain). In the clarithromycin group, the following events were associated with discontinuations in more than one patient: vomiting (5 patients), nausea and diarrhea (4 patients each) and abdominal pain, anxiety and rash (2 patients each). No other event was associated with premature discontinuation more than once. One patient in the clarithromycin treatment group, number 730 (study center 15), experienced a prolonged QT interval.

MO COMMENT: When premature discontinuation of study drug was considered, a smaller proportion of the total number of patients treated with BAY 12-8039 was unable to complete therapy than was the proportion of patients treated with clarithromycin (2.5% v. 5.0%). Of these discontinuations, 4 of 6 (67%) patients treated with BAY 12-8039 discontinued because of an adverse event related to the gastrointestinal system (patients no. 87, 97, 114, and 350), while 7 of 12 (58%) treated with clarithromycin discontinued because of same (patients no. 102, 124, 148, 424, 473, 479, and 745).

MO COMMENT: Another patient treated with BAY 12-8039 (no. 409) discontinued study drug on day 3 of treatment after 1 day of abnormal thinking, which was described by the investigator as difficulty thinking and writing. The sixth patient treated with BAY 12-8039 who discontinued study drug prematurely did so on day 9 of treatment because of chest pain.

In addition to the 18 patients listed as prematurely discontinued from study medication, there were an additional 5 patients prematurely discontinued in the study (no. 123, 379, 327, 240, and 911) who had adverse events with action taken by the investigator including study drug discontinuation. However, on the End of Study Information CRF page that determined the reason for discontinuation of the patient from the study, the reason given for discontinuation was in each case something other than adverse event (patients no. 123, 379 and 327: insufficient therapeutic effect; patient no. 240: consent withdrawn; and patient no. 911: investigator's request). For the above reason, these 5 patients were not included as premature discontinuations due to adverse events in text Table IV (Section 12.2.1) and in Table 14.3.1/1. Including these 5 patients in the analysis of premature discontinuations due to adverse event gives a total of 9 patients in the BAY 12-8039 group and 14 in the clarithromycin group.

MO COMMENT: Because all three of the above reasons for discontinuation could result from the patient experiencing one or more adverse effects, an analysis of premature discontinuations should include the possibility that the true rate of discontinuations in the BAY 12-9039 group was 3.8% and in the clarithromycin group was 5.9%.

Serious adverse events

A total of 23 patients in this study experienced serious adverse events, 9 in the BAY 12-8039 treatment group and 14 in the clarithromycin treatment group. In 10 cases (3 BAY 12-8039 and 7 clarithromycin) the serious adverse events did not occur until after the end of study drug therapy.

In the BAY 12-8039 group, the most common serious adverse events were congestive heart failure (3 events), pleural effusion (3 events) and pneumonia (2 events). One patient in the BAY 12-8039 treatment group had an adverse event of diarrhea assessed as serious by the investigator, and 1 patient had a worsening of atrial fibrillation, also assessed by the investigator as serious. In the clarithromycin treatment group, pneumonia (3 events) and various cardiovascular events (7 events) were the most common. Two patients in the clarithromycin group were responsible for the 3 pneumonia events characterized as serious adverse events. Of the cardiovascular events in the clarithromycin group, 2 were related to episodes of QT prolongation (both in patient No. 730 from center 15; see above). This patient also experienced extrasystoles and non-sustained ventricular tachycardia. Digestive events (intestinal obstruction) were observed in only 1 patient in the clarithromycin group. Two CNS events (1 coma and 1 CNS neoplasia) were observed in the clarithromycin group.

MO COMMENT: Review of the serious adverse events did not provide any additional information regarding the safety profile of BAY 12-8039 in the study under review. Four of the seven serious cardiovascular events in the clarithromycin group occurred in one patient (no. 730).

Laboratory abnormalities

Table 11 presents incidence of high and low clinical chemistry and hematology parameters that occurred in at least 5% of patients.

Table 11. Incidence of laboratory abnormalities occurring in at least 5% of any treatment group

Lab Variable	BAY 12-8039 400 mg	Clarithromycin
High		
MCH	9/201 (4%)	11/200 (6%)
WBC	6/110 (5%)	9/111 (8%)
Neutrophils (segs)	6/113 (5%)	12/117 (10%)
Neut (segs) absolute ct	2/118 (2%)	10/110 (9%)
Lymphocytes	11/217 (5%)	18/226 (8%)
Monocytes	10/217 (5%)	13/222 (6%)
Eosinophils	23/211 (11%)	20/217 (9%)
Platelets	33/204 (16%)	38/212 (18%)
PT	21/153 (14%)	14/156 (9%)
APTT	17/182 (9%)	18/186 (10%)
Serum glucose	39/172 (23%)	46/168 (27%)
Phosphorus, inorg	23/220 (10%)	24/221 (11%)
Chloride	24/218 (11%)	15/224 (7%)
C-reactive protein	5/ 32 (16%)	12/ 40 (30%)
SGOT/AST	9/205 (4%)	13/217 (6%)
SGPT/ALT	17/206 (8%)	19/208 (9%)
GGT	10/178 (6%)	16/184 (9%)
Alkaline phosphatase	10/208 (5%)	3/213 (1%)
Cholesterol, total	47/162 (29%)	54/163 (33%)
Triglycerides	56/200 (28%)	53/195 (27%)
Low		
Hematocrit	32/191 (17%)	33/192 (17%)
Hemoglobin	34/188 (18%)	25/190 (13%)
RBC	20/112 (18%)	9/103 (9%)
MCHC	14/205 (7%)	15/207 (7%)
WBC	7/217 (3%)	10/219 (5%)
Neutrophils (segs)	10/219 (5%)	10/226 (4%)
Neut (segs) absolute ct	14/217 (6%)	10/218 (5%)
Lymphocytes	5/100 (5%)	7/100 (7%)
Uric acid	21/191 (11%)	13/173 (8%)
Phosphorus, inorg	5/197 (3%)	13/206 (6%)
Bicarbonate (HCO3)	12/221 (5%)	9/216 (4%)
BUN	12/210 (6%)	7/206 (3%)
Amylase	11/190 (6%)	7/195 (4%)

Patients in the BAY 12-8039 group had a somewhat higher incidence of elevated PT time (14% vs. 9%) and higher incidence of low hemoglobin (18% vs. 13%) and RBCs (18% vs. 9%). Patients in the clarithromycin group had a higher incidence of elevated C-reactive protein (30% vs. 16%), neutrophils (10% vs. 5%) and of proteinuria (29% vs. 23%).

> MO COMMENT: The significance of these differences is perhaps best understood in the context of the review of the safety database for the entire NDA. The higher incidence of low hemoglobin and low RBC counts among patients treated with BAY 12-8039 is noteworthy considering the observations of bone marrow toxicity in animals exposed to 12-8039. For further discussion, the reader is referred to the review of the Integrated Summary of Safety.

REVIEWER'S COMMENTS

Bay 12-8039 400 mg daily for 10 days demonstrates clinical efficacy equivalent to that of clarithromycin 500 mg bid for 10 days in the treatment of ambulatory patients with community-acquired pneumonia. Clinical efficacy in the treatment of pneumonia caused by the organisms *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, and *C. pneumoniae* was adequately demonstrated in this study. Clinical efficacy in the treatment of pneumonia due to *S. pneumoniae* non-susceptible to penicillin was suggested by the successful outcomes in a small number of patients infected with these organisms. This study of ambulatory patients did not provide data on the clinical efficacy of moxifloxacin in the treatment of pneumonia due to *S. aureus* or *K. pneumonaie*. The gastrointestinal adverse event profile for BAY 12-8039 400 mg daily is comparable to that of clarithromycin 500 mg bid. The significance of isolated neuropsychiatric events and hematologic laboratory abnormalities are perhaps best understood in the context of the Integrated Summary of Safety.

Study No. 0140

A multicentre, multinational, transregional, prospective, randomised, double-blind study to compare the efficacy and safety of BAY 12-8039 oral tablets to amoxicillin oral capsules in the treatment of adult patients with suspected community-acquired pneumococcal pneumonia

STUDY DESIGN

This equivalence study was conducted at 82 centers outside the United States from June 1997 to June 1998. The centers were divided into four main regions: 1) France (30 centers), 2) Latin America (11 centers in Argentina, Brazil, Chile, Mexico, and Uruguay), 3) Eastern Europe (25 centers in Croatia, Czech Republic, Hungary, Russia, Slovenia, Turkey, Ukraine), 4) Other countries (16 centers in Estonia, Hong Kong, Lithuania, Portugal, South Africa, Spain, United Kingdom). Moxifloxacin 400 mg daily for 10 days was compared in a 1:1 randomization to an approved comparator, amoxicillin 1000 mg tid for 10 days, for both efficacy and safety in the treatment of CAP in both out-patients and in-patients. The approved dose of amoxicillin [redacted] for the treatment of lower respiratory tract infection (LRTI) in the US differs from the dose used as a comparator in this study. For mild to moderate LRTI the approved dose is 875 mg q 12 hours, for severe LRTI it is 500 mg q 8 hours. No duration of therapy is provided in the label. The US approved label of [redacted] also specifies that this agent is approved only for LRTI due to *Streptococcus* species (α- and β- hemolytic only), *S. pneumoniae, Staphylococcus* species, and *H. influenzae.* In the study report for #0140, the applicant noted that there are a number of different doses of amoxicillin used to treat pneumonia, and stated that the dose used in this study is the dose recommended in some European guidelines to ensure adequate concentrations of amoxicillin in patients infected with strains of *S. pneumoniae* with reduced susceptibility to penicillin.

> MO COMMENT: The geographic regions included in this study provide an opportunity to evaluate the efficacy of both agents in developed and developing countries and in areas such Eastern Europe, Spain, and South Africa which have been shown to have high rates of penicillin-resistant pneumococcal isolates.

> MO COMMENT: The applicant selected a higher dose than that approved in the US for amoxicillin for the treatment of CAP. This dose of the comparator agent provides a more stringent assessment of moxifloxacin efficacy for this indication. However, the use of this higher dose of amoxicillin for CAP cannot be used to substantiate any potential claims of an enhanced safety profile for moxifloxacin compared with amoxicillin.

> MO COMMENT: This study enrolled both ambulatory and hospitalized patients with CAP. As noted in the introduction to the MO review of study #D96026, the published literature suggests that etiologic agents may differ in these two populations as characterized in the US, Canada, and Western Europe. Atypical pathogens such as *M. pneumoniae* and *C. pneumoniae* account for a larger proportion of CAP in out-patients, while *S. pneumoniae* continues to be the most

commonly isolated pathogen in in-patients with CAP. The label for [redacted] points out that this drug is only active against 'typical' bacterial pathogens, though some of these are much less commonly isolated from patients with community-acquired infections than they were in earlier decades. Analysis of amoxicillin efficacy in the treatment of CAP in out-patients compared with that in in-patients is a means of testing this hypothesis of differing microbiologic etiologies. Alternatively, such an analysis could suggest that cure rates are independent of microbiologic etiology. For further discussion of these issues, the reader is referred below to RESULTS, Evaluability and efficacy, MO assessment.

Patients aged 18 years or older with signs and symptoms consistent with suspected pneumococcal pneumonia were eligible for enrollment. Patients were treated as in-patients or out-patients at the discretion of the investigator. In order to be classified as having CAP, patients must have had evidence of the following:

- Fever (core T $\geq$ 38.5° or oral T $\geq$ 38°C)
- Radiologic evidence of an infiltrate consistent with pneumonia
- One or more of the following: cough, purulent sputum, dyspnea or tachypnea, auscultatory findings such as rales/rhonchi indicating pulmonary consolidation

The inclusion criteria also included certain findings that were thought to be indicative of pneumococcal infection. The following text is taken verbatim from the protocol:

> *At least two of the following criteria must lead to suspect pneumococci as the causative agent of CAP:*
> - *Rapid onset of symptoms (within 48 hours prior to inclusion)*
> - *Temperature $\geq$ 39 °C (or oral temperature $\geq$ 38.5 °C) accompanied by rigors/chills*
> - *Pleuritic chest pain*
> - *Chest x-ray showing a systematised infiltrate*
> - *Gram positive cocci on a direct sputum stain*

Neither the protocol nor the study report explained how patients with these additional findings thought to be indicative of pneumococcal infection were handled. It does not appear that patients had to have these additional findings to be enrolled in study #0140. In a telephone conversation with Dr James Williams, Bayer, 9/17/99, it was explained that patients had to have two or more of the five findings suggestive of pneumococcal infection in order to be eligible for the study.

Exclusion criteria of note were patients with severe cardiac failure (NYHA Class IV), patients with severe respiratory tract infections requiring parenteral therapy or mechanical ventilatory support, patients with suspected aspiration pneumonia, patients hospitalized more than 48 hours, patients with significant liver impairment (SGOT,

SGPT, and/or total bilirubin >3x upper limit of normal), patients with significant renal impairment (Cr >3.0 mg/dl or Cr clearance <30 cc/min), and patients with coexistent disease thought likely to affect the outcome of the study, including lung cancer, lung abscess, connective tissue disease affecting the lungs, empyema. A protocol amendment (dated 5/97) also excluded patients with prolonged QT interval on EKG or patients taking medication reported to increase the QT interval.

> MO COMMENT: Factors that determine whether or not a patient is to be hospitalized for a given illness can vary according to setting. Severity of illness, availability of resources, cultural perceptions of hospitalization, and local practice patterns can all affect whether a patient is managed in or out of the hospital. Because the decision to hospitalize was not standardized in this study, but rather left to the individual investigator, characteristics of the groups of ambulatory and hospitalized patients may vary widely and may only permit limited conclusions regarding these categories of CAP.

> MO COMMENT: The draft label submitted by the applicant does not distinguish among degrees of severity of CAP. The study under review included hospitalized patients, but all were candidates for oral therapy.

In addition to the clinical and radiologic evaluations described above, certain laboratory tests were performed prior to enrollment. Two aliquots of blood were taken for culture from each patient at enrollment. Specimens of sputum were obtained for gram stain and culture from all patients who were able to provide one. Transtracheal aspirates, bronchoscopic washings or brushings, and pleural fluid were also obtained when necessary for gram stain and culture. Serum samples were obtained and frozen at admission to the study for serologic testing for *Legionella pneumophila, Chlamydia pneumoniae, Chlamydia psittaci, and Coxiella burnetti.* All serologic testing was performed at a central reference laboratory. Routine hematology (complete blood count or CBC) serum chemistries, and urinalysis were also performed. ECGs were performed at enrollment and at specified time points during the treatment period. During the course of the study, any additional testing or use of therapeutic adjuncts including blood gas determination, CT scan, bronchoscopy, and supplemental oxygen administration were also recorded in the case report form.

Once randomized and started on treatment, patients were instructed to return on Day 3-5 of treatment (During Therapy Visit), Day 3-5 post-treatment (End of Therapy Visit or EOT), and Day 21-28 post-treatment (Follow-up Visit or F/U). Clinical, laboratory, and compliance assessments were made at these visits.

Patients were considered evaluable for efficacy analysis (per protocol population) if they met the clinical criteria for the diagnosis of CAP as noted above, if no other systemic antibacterial agents were administered concomitantly with the study drug, if study drug were given for a minimum of 48 hours if the result of therapy were a failure, or a minimum of 5 days if the result were a success, if compliance with dosing were $\geq$ 80%, if there were no protocol violations which influenced treatment efficacy, if the random code

were not broken, if there were no missing or 'indeterminate' essential data which could not be recovered.

The primary efficacy variable was the clinical response in the per protocol population at the EOT Visit (3-5 days following the completion of therapy). Possible outcomes at this point included clinical cure, clinical failure, and indeterminate. Reasons for an indeterminate assessment had to be fully documented in the case report form.

> MO COMMENT: The use of the EOT visit as the primary efficacy endpoint for this study is not consistent with FDA guidelines for CAP studies set forth in either the 1992 Points to Consider Document and the 1997 Draft Guidance for Industry. The applicant pointed out that this study, conducted outside the US, was undertaken using European regulatory guidelines that warranted that theTOC be assessed at this early post-treatment visit. The pharmacokinetics of moxifloxacin warrant some review when considering what can be learned from this visit. The t1/2 is approximately 12 hours at the end of a 10-day dosing regimen, at which time the plasma Cmax is 4.5mg/L (µg/ml). It has been shown that tissue concentrations can far exceed plamsa levels. In the bronchial mucosa, Cmax has been shown to be ~1.7x plasma concentration; in the alveolar macrophages, Cmax has been shown to be ~18x plasma concentration. The MIC_{90} of moxifloxacin for *S. pneumoniae* strains isolated in the clinical studies of the NDA was 0.25 µg/ml. Three to five days following the completion of a 10-day course of therapy represents six to ten half-lives of drug. In the alveolar macrophage, moxifloxacin levels range from [redacted] µg/ml during this period. Patients with pneumococcal pneumonia who were evaluated during the 3-5 day interval following the completion of therapy would still have had drug levels above the MIC of the infecting organism in some tissue compartments of the lung, and late failures would not be included in this population. For this reason, the MO analysis also included an evaluation of clinical cure in the PP population at the F/U visit 21-28 days following the completion of therapy. See RESULTS, Evaluability and efficacy, MO assessment.

> MO COMMENT: MO analyses included clinical outcome at the F/U visit by site of care (ambulatory v. hospitalized), clinical outcome in microbiologically evaluable patients infected with *S. pneumoniae* strains susceptible, non-susceptible, and resistant to penicillin, and clinical outcome in patients with positive blood cultures.

STUDY RESULTS

Demographics

There were 411 patients enrolled in this study; 203 were treated with BAY 12-8039 and 208 with amoxicillin. Demographic characteristics of patients in both treatment arms are

presented in Table 1. The groups were well matched for gender, race, age, weight, and smoking history.

Table 1. Demographic variables at enrollment by treatment group

	BAY 12-8039	Amoxicillin
Sex, % female	39.5%	38.0%
Age (Yrs), Mean	51.5	50.4
Weight (kg), Mean	68	69.3
Cigarette smoker	58.0%	56.7%
Febrile (Tcore ≥38.5° C)	95.5%	97.6%
Temperature (° C), Mean	39.2	39.3
Respiratory rate (/min), Mean	24	24
Hospitalization pre-therapy	79.0%	78.4%

MO COMMENT: Over three-fourths of patients in this study were hospitalized. Almost all were febrile at presentation. This study population was sicker than the study population of #D96026, which was all out-patients.

Evaluability and efficacy
Clinically evaluable population
Applicant assessment

Table 2 presents the applicant's analysis of clinical outcome in those patients who were clinically evaluable for efficacy analysis. As noted above, inclusion in this study population did not require that a microbiologic etiology of the patient's infection be identified.

Table 2. Clinical response in clinically evaluable population at 3-5 days post therapy (EOT)- applicant assessment

	BAY 12-8039	**Amoxicillin**
Total	177 (100.0%)	185 (100%)
Clinical Cure	162 (91.5%)	166 (89.7%)
Clinical Failure	15 (8.5%)	19 (10.3%)

The 95% CI around the difference in cure rates was reported by the applicant as (-4.2, 7.8). The 95% CI with continuity correction factor calculated by the MO was (-4.8, 7.8). The applicant's assessment of cure rates at the EOT visit meets the statistical requirement for demonstrating equivalence with an approved comparator. As noted above, the pharmacokinetics of moxifloxacin suggest that at the EOT visit, a significant proportion of patients may have tissue levels of moxifloxacin above the MIC for *S. pneumoniae*. Thus assessment of cure rates at EOT may not provide information about late failures in pneumococcal pneumonia. In the study report for study # 0140, the applicant noted that the range of the 'real end of therapy visits' was day –3 (3 days before stopping therapy) to day +16, and that the range of the 'real follow-up visits' was day +8 to +50. (NDA 21-085, vol 284, page 92).

Clinically evaluable population
MO assessment
Clinical efficacy
The MO analysis of clinical efficacy of BAY 12-8039 in CAP addressed the following questions:

- clinical outcome in clinically evaluable patients, including a comparison between the EOT population (applicant analysis) and the F/U population (MO analysis)
- clinical outcome in clinically evaluable patients- ambulatory vs. hospitalized patients
- clinical outcome in clinically and microbiologically evaluable patients
- clinical outcome in patients with CAP due to *S. pneumoniae* and positive blood cultures
- clinical outcome in patients with CAP due to *S. pneumoniae* including penicillin-R and penicillin-I strains

The discussions of clinical efficacy in clinically evaluable populations are presented here. The discussions of clinical efficacy in microbiologically and clinically evaluable populations are presented in the subsection that follows.

Evaluability and efficacy in the clinically evaluable population were assessed by the MO using a sampling technique. A random sample of approximately 25% of the study population was generated. Individual CRTs and pertinent databases were reviewed by the MO for agreement between the MO and applicant regarding evaluability and outcome. The MO assessed patient evaluability and efficacy with the same general scheme as that used for study #D96026 (see MOR study #D96026).

Review of the sample as described above resulted in reclassification by the MO of four patients in the moxifloxacin treatment group and two patients in the amoxicillin treatment group. One patient who received BAY 12-8039 was considered unevaluable by the applicant and was reclassified as a failure by the MO. Three patients treated with BAY 12-8039 and two patients treated with amoxicillin were considered cures by the applicant and were reclassified as unevaluable by the MO. Analysis of these changes demonstrated adequate agreement with the applicant's findings such that the MO accepted the applicant's assessment of the primary efficacy endpoint, evaluability and clinical outcome of the clinically evaluable population at the EOT visit. These data, presented above in Table 2, demonstrate a high efficacy rate for moxifloxacin in the treatment of CAP that is shown to be statistically equivalent to that of an approved comparator, amoxicillin. The lower bound of the 95% CI around the difference in point estimates of efficacy rates if >-10%. As noted above, 1) the dose of amoxicillin used in the study under review (1000 mg tid x 10 days) was twice that of the approved dose for community acquired pneumonia (500 mg tid) and 2) the endpoint at which the applicant assessed clinical efficacy was a time at which patients may still have had clinically significant drug levels.

Clinical efficacy at F/U v. EOT

The MO performed an additional analysis of clinical outcome in the clinically evaluable population, the follow-up visit originally scheduled at 21-28 days post therapy (F/U) was used as the endpoint. The MO accepted the applicant's assessment of a clinically evaluable patient and included any patient who returned ≥ 14 days following the completion of therapy. Table 3 presents the results of the MO analysis at the F/U visit.

Table 3. Clinical response in clinically evaluable population at ≥14 days post therapy (F/U visit)- MO assessment

	BAY 12-8039	Amoxicillin
Total	160 (100.0%)	178 (100%)
Clinical Cure	143 (89.3%)	159 (89.3%)
Clinical Failure	17 (10.6%)	19 (10.6%)

Using the more stringent criterion of F/U visit as the TOC, the MO analysis found clinical efficacy rates to be comparable to those noted in the applicant analysis. The 95% confidence interval around the difference in these cure rates of {-7.1, 7.2} meets the criterion for the demonstration of clinical equivalence of these two treatments for community acquired pneumonia.

Clinical efficacy in hospitalized v. ambulatory patients

Of the 411 patients enrolled in the study under review, 321 (78%) were hospitalized at the time of presentation with community acquired pneumonia. Such a population permits an analysis of drug efficacy in hospitalized patients that can be compared to efficacy in ambulatory patients. It should be borne in mind that study #0140 was conducted outside the US using oral formulations of two antimicrobials. Current medical (insurer) practice in the US does not generally result in the hospitalization of patients who are treated with oral drugs. Nonetheless, the study population in #0140 can be analyzed to compare drug efficacy in a group of patients with more severe CAP with efficacy in patients who are managed on an ambulatory basis. Table 4 presents the MO analysis of clinical efficacy in clinically evaluable patients at follow-up by hospitalization status.

Table 4. Clinical efficacy in clinically evaluable patients at F/U visit by hospitalization status at presentation- MO analysis

	BAY 12-8039	AMOXICILLIN
HOSPITALIZED PTs		
No. evaluable	122	141
No. cure (%)	107 (87.7)	125 (88.6)
AMBULATORY PTs		
No. evaluable	35	36
No. cure (%)	34 (97.1)	34 (94.4)

Table 4 shows that clinical efficacy rates observed for BAY 12-8039 400 mg q day x 10days in hospitalized and ambulatory patients are equivalent to those observed for

amoxicillin 1000 mg tid x 10 days. It also shows that efficacy rates for both agents are slightly higher in out- patients compared with in-patients. This may be explained by the higher degree of severity of illness in patients who are admitted to the hospital. Whether it provides any information about drug efficacy against certain etiologic agents is discussed below in the section entitled Microbiologic and Clinically Evaluable Population.

Microbiologically and clinically evaluable population
Applicant assessment

Table 5. presents the applicant's assessment of clinical efficacy in microbiologically and clinically evaluable patients by infecting organism.

Table 5. **Clinical Resolution Rates of Proposed Dosing Regimen at the Test-of-Cure (EOT) Visit by Organism**

	BAY 12-8039 400 mg q D	Amoxicillin 1000 mg tid
Streptococcus pneumoniae	35/42 (83%)	37/43 (86%)
Haemophilus influenzae	7/7 (100%)	14/17 (76%)
Mycoplasma pneumoniae	6/6 (100%)	11/12 (92%)
Chlamydia pneumoniae	4/5 (80%)	1/1 (100%)
Staphylococcus aureus	3/3 (100%)	3/4 (75%)
Moraxella catarrhalis	0/1 (0%)	1/2 (50%)
Klebsiella pneumoniae	2/3 (67%)	2/2 (100%)

Clinical efficacy of BAY 12-8039 in patients infected with *S. pneumoniae* was comparable to that observed for amoxicillin. It is noteworthy that efficacy rates for both treatment groups infected with this organism were lower than those reported in study #D96026, a US based study of ambulatory patients. There were relatively small numbers of isolates of species other than *S. pneumoniae*. These are best understood when compared with the other studies for this indication. The reader is referred to the CONCLUSIONS section of the MOR for the CAP indication.

MO assessment
Clinical efficacy in CAP due to *S. pneumoniae* and penicillin-resistant strains of *S. pneumoniae*
Bacteremic v. non-bacteremic patients

According to data submitted by the applicant in the original NDA, there were 85 patients in study #0140 identified by the applicant as infected with *S. pneumoniae.* Nineteen of these patients had positive blood cultures, 75 had positive respiratory cultures. Table 6 presents clinical efficacy among patients infected with *S. pneumoniae* by body site and treatment arm.

Table 6. Clinical efficacy among patients infected with *S. pneumoniae* by body site- MO analysis

	BAY 12-8039	Amoxicillin
Positive blood culture	6/9 (66.7%)	10/10 (100.0%)
Positive respiratory culture	32/38 (84.2%)	31/37 (83.7%)

The small numbers of patients with pneumococcal bacteremia must be considered when evaluating the data presented in Table 6. However it is noteworthy that the clinical efficacy rate of BAY 12-8039 in patients with pneumococcal pneumonia and bacteremia (66.7%) is lower than that observed for 12-8039 for all patients with pneumococcal pneumonia (83%) and for all patients with community acquired pneumonia (91.7%). A distinction between out-patients and in-patients may be a way to address this discrepancy. Bacteremic patients with *S. pneumoniae* CAP are more likely to be sick enough to be admitted to the hospital. Until more is known about drug efficacy in patients with *S. pneumoniae*, it may be prudent to limit the use of moxifloxacin to patients with CAP of mild to moderate severity.

Clinical efficacy in the treatment of CAP due to PCN-R and PCN-I *S. pneumoniae*

The reader is referred to the MOR of study #D96026, Microbiologically and clinically evaluable population, MO assessment for a discussion of the demonstration of clinical efficacy against strains of *S. pneumoniae* that are resistant to penicillin. It should be noted that the definition of penicillin resistance for *S. pneumoniae* strains isolated in study #0140 was MIC > 1.0 μg/ml. The definition of penicillin resistance for pneumococcal isolates currently advocated by both CDC and NCCLS and used by FDA is MIC ≥ 2.0 μg/ml. There is a growing consensus at both CDC and NCCLS that this breakpoint should be changed to 4.0 μg/ml for pneumococcal infections other than meningitis.

The applicant submitted additional data at the request of the MO on September 22, 1999 in which all patients from whom *S. pneumoniae* was isolated in blood or respiratory cultures at pre-treatment were identified. This additional submission listed 81 such patients. Nine of them were infected with *S. pneumoniae* strains for which the MIC of penicillin was ≥ 2.0 μg/ml. Six of these patients were treated with BAY 12-8039 and three were treated with amoxicillin. All six of the patients in the BAY 12-8039 treatment group had *S. pneumoniae* isolated from respiratory specimens. Two of the three patients in the amoxicillin treatment group had *S. pneumoniae* isolated from the blood. Table 7 presents clinical efficacy rates for both agents in patients infected with strains of *S. pneumoniae* that were resistant to penicillin (MIC ≥ 2.0 μg/ml). Of the nine penicillin-resistant (PCN-R) pneumococcal isolates, eight had a MIC of PCN 2.0 μg/ml, and one had a MIC of PCN 8.0 μg/ml.

Table 7. Clinical efficacy in patients infected with PCN-R *S. pneumoniae* (MIC ≥ 2 μg/ml)

	BAY 12-8039 400 mg q d	Amoxicillin 1000 mg tid
No. evaluable	6	3
No. cure (%)	4 (66.7)	3 (100.0)

Data from this small number of patients are not conclusive, but suggest that BAY 12-8039 may not achieve the same cure rates as high dose amoxicillin in the treatment of pneumococcal pneumonia caused by PCN-R strains. Larger numbers of patients infected with such strains would be needed to evaluate BAY 12-8039 efficacy in this subpopulation. Clinical efficacy data from patients infected with strains with intermediate susceptibility to penicillin (I > 0.1 and < 2.0 μg/ml) may also provide some information about the efficacy of BAY 12-8039 in the treatment of pneumococcal pneumonia due to bacterial strains that are non- susceptible to penicillin. Table 8 presents such data.

Table 8. Clinical efficacy in patients infected with *S. pneumoniae* with intermediate (I) susceptibility to penicillin (MIC >0.1, < 2.0 μg/ml)

	BAY 12-8039 400 mg q d	Amoxicillin 1000 mg tid
No. evaluable	12	11
No. cure (%)	11 (91.7)	9 (81.8)

Data from this small number of patients suggest that BAY 12-8039 may be as effective as amoxicillin in the treatment of pneumococcal pneumonia due to PCN-I strains. The available data do not support the conclusion that BAY 12-8039 is as effective as high-dose amoxicillin in the treatment of CAP due to PCN-resistant strains of *S. pneumoniae.*

Safety

Extent of exposure

Of the 411 patients enrolled in the study, 408 received at least one dose of study medication and were thus evaluable for safety. The entire course of study drug therapy was completed by 76% of the patients who received moxifloxacin and by 71% of the patients who received amoxicillin.

Adverse events

Table 9 compares various adverse event rates between the BAY 12-8039 and amoxicillin treatment groups. These rates were similar for each group. It should be noted that the dose of amoxicillin used in the study under review was twice the labeled dose for community-acquired pneumonia.

Table 9. Summary of adverse events

	BAY 12-8039 400 mg (N=200)	**Amoxicillin(N=208)**
Any Adverse Event	118 (59%)	102 (49%)
Any Drug-Related Event	71 (35.5%)	60 (28.8%)
Any Serious Event	23 (11.5%)	19 (9.1%)
Discontinued due to AE	8 (4.0%)	8 (3.8%)
Died	3 (1.5%)	4 (1.9%)

Adverse event rates that occurred in at least 2% of either treatment group are presented in Table 10, and treatment-related adverse event rates that occurred in at least 2% of either treatment group are presented in Table 11.

Table 10. Incidence of adverse events occurring in at least 2% of any treatment group

	BAY 12-8039 Rate (%)	Amoxicillin Rate (%)
Liver function tests abnormalities	6.0	11.1
Diarrhoea	8.5	5.8
Nausea	7.0	1.0
Headache	5.0	2.9
Vomiting	5.5	1.0
GGT increased	1.5	4.8
Pneumonia	3.0	2.4
Rash	3.0	2.4
Bronchitis	2.5	2.4
Thrombocythemia	1.5	3.4
Hypertension	3.5	1.0
Amylase increased	2.0	2.4
Eosinophilia	1.5	2.9
Abdominal pain	2.5	1.4
Chest pain	2.5	0.5
Hypotension	2.0	1.9
Anaemia	2.0	1.0
Heart failure	2.0	not reported

Table 11. Incidence of treatment-related adverse events occurring in at least 2% of any treatment group

	BAY 12-8039 Rate %	Amoxicillin Rate %
Liver function tests abnormalities	6.0	10.6
Diarrhoea	7.5	4.3
Nausea	7.0	1.0
GGT increased	1.5	4.8
Vomiting	4.0	1.0
Amylase increased	2.0	2.4
Headache	3.0	1.4
Eosinophilia	1.5	2.4
Thrombocythemia	1.5	

Rash	2.0	1.4
Abdominal pain	2.5	0.5

MO COMMENT: The MO reviewed the complete line listings for all adverse events and all treatment-related adverse events. An additional noteworthy finding was the incidence of drug-related cholestatic jaundice, which was noted in 1.5% (3/200) patients treated with moxifloxacin and in 0.5% (1/208) patients treated with amoxicillin.

The most common drug-related adverse events in the BAY 12-8039 group were diarrhea (7.5%), nausea (7%), and vomiting (4%). Liver function test abnormalities were also seen with relatively high frequency in this group, though not with as high a frequency as in the amoxicillin group. The most common drug-related adverse events in the amoxicillin group were liver function test abnormalities (all LFTs 10.6%, GGT 4.8%), and diarrhea (4.3%).

MO COMMENT: The most common drug-related AEs observed for moxifloxacin and the rates at which they occurred in the present study were similar to those reported for study #D96026. Of note was also the reports of drug related cholestatic jaundice in patients treated with moxifloxacin.

Deaths and serious adverse events
There were seven deaths reported in this study. Three patients died in the moxifloxacin treatment group and four patients died in the amoxicillin treatment group. None of these deaths was related to study drug.

MO COMMENT: The MO reviewed the narratives of each of the above patients' courses and concurs with the above conclusions.

A total of 16 patients were prematurely discontinued from study drug therapy due to adverse events, eight in the BAY 12-8039 treatment group and eight in the amoxicillin treatment group. Reasons for discontinuations in the BAY 12-8039 group included persistence or worsening of pneumonia (3 patients), rash (3 patients), uremia, abdominal distention, diarrhea, and heel pain (1 patient each). For three patients, two AEs each were reported as reasons for discontinuation. In the amoxicillin group, the following events were associated with discontinuations: worsening pneumonia (2 patients), abnormal liver function tests (2 patients), cutaneous allergy (2 patients), and apnea, leukopenia, thrombocyotpenia, and convulsion (1 patient each). For three patients, two AEs each were reported as reasons for discontinuation.

MO COMMENT: Interestingly, gastrointestinal complaints were less common reasons for discontinuation in the present study as compared with #D96026, reviewed above. Worsening of pneumonia (failure of therapy) was one of the most common reasons for study drug discontinuation in both treatment groups in the present study. The sicker, largely hospitalized patient population on study #0140 may explain this observation.

Serious adverse events

A total of 42 patients in this study experienced serious adverse events, 23 (11.5%) in the BAY 12-8039 treatment group and 19 (9.1%) in the amoxicillin treatment group. The applicant reported that all reported serious AEs in the moxifloxacin group except for worsening of pneumonia , noted in patients #10074 and #10321, were considered unrelated to study drug. The applicant reported that the following patients in the amoxicillin treatment group experienced serious AEs that were possibly or probably drug related: acute renal failure and agitation, # 10137; seizures, #10254; pneumonia relapse #10328; rash, #10497; liver function test abnormalities, #10517.

MO COMMENT: The MO reviewed the narratives for patients with serious AEs and found that there were two patients in the BAY 12-8039 treatment group who developed empyemas (both had pneumococcal bacteremia), and two who developed worsening of pneumonia (*S. pneumoniae* grew from sputum) whose serious AEs were considered by the applicant to be unrelated to study drug. Review of these cases suggested that all three of these patients' deteriorations were related to study drug. The MO was unable to determine why the applicant considered some clinical deteriorations attributable and others unattributable to study drug.

MO COMMENT: Review of the serious adverse events did not provide any additional information regarding the safety profile of BAY 12-8039 in the study under review. There was one patient who was treated with BAY 12-8039 who had an episode of ventricular fibrillation and died 52 days after completion of study drug. The MO reviewed this case and concurred that these events were not related to study drug.

Laboratory abnormalities

The MO reviewed the line listings of high and low chemistry and hematology abnormalities that occurred in at least 10 patients of at least one treatment group. Of note were comparable rates of high values for SGOT, SGPT, and alkaline phosphatase for the two treatment groups. High SGOT seen 20.8% and 25.5%, high SGPT seen 28.7% and 33.3%, high alk phos seen 10.1% and 13.4% of BAY 12-8039 and amoxicillin treatment groups, respectively. There were no clinically significant differences in rates of high laboratory values.