

subject was considered a study treatment failure or the antimicrobial agent was not considered to have had an effect on the infection.

- The subject did not receive any interfering therapeutic procedures or any other potential confounding intervention during the study unless the subject was considered a treatment failure.
- The subject did not violate any selection criteria unless it was considered not to affect the efficacy evaluation.
- An efficacy evaluation was conducted 7-23 days posttreatment (Test-of-Cure Visit) unless the subject was a treatment failure prior to this time.

Clinically and Bacteriologically Evaluable Subject Population

In addition to the above conditions, subjects must have had at least one target pathogen (*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *H. parainfluenzae*, or *S. aureus*) isolated at pretreatment based on an acceptable gram stain (≤ 10 squamous epithelial cells and ≥ 25 polymorphonucleated leukocytes per low power field).

Intent-to-Treat Subject Population

All subjects who took at least one dose of study drug and had a clinical diagnosis of AECB at pretreatment were included in the intent-to-treat subject population.

All Treated Subjects Population

All subjects who took at least one dose of study medication were included in the all treated subjects population.

Disposition of Subjects by Data Sets

Three hundred seventeen (317) subjects were randomized to and took clarithromycin ER and 303 were randomized to and took clarithromycin IR. Four hundred thirty-eight (217 clarithromycin ER and 221 clarithromycin IR) subjects were excluded from the clinical and bacteriological analyses of efficacy. Of these, 374 (181 clarithromycin ER and 193 clarithromycin IR) subjects did not have a target pathogen isolated at pretreatment. Of the remaining 64 subjects who were excluded, 40 subjects did not meet the selection criteria, 13 subjects were enrolled by an investigator who subsequently was disqualified, six subjects did not return for the Test-of-Cure Visit, four subjects used confounding medications, and one subject was noncompliant with the treatment regimen.

One hundred (56 clarithromycin ER and 44 clarithromycin IR) subjects were excluded from the clinical efficacy analyses. Forty subjects were excluded because they did not meet selection criteria, 21 subjects were excluded because they did not return for the Test-of-Cure Visit, 17 subjects used confounding medication, 13 subjects were enrolled by an investigator who subsequently was disqualified, seven subjects were noncompliant with the treatment regimen, and two subjects returned for the Test-of-Cure Visit outside the allowable window (13-23 days posttreatment). Several of the subjects excluded from the clinically and bacteriologically evaluable analyses for no pretreatment pathogen were excluded from the clinically evaluable analyses for other reasons.

Thirty-five (17 clarithromycin ER and 18 clarithromycin IR) subjects were excluded from the intent-to-treat efficacy analyses. Twenty-two subjects did not have a clinical diagnosis of AECB, such as no evidence of chronic bronchitis, pneumonia/positive x-ray at pretreatment, and one immunocompromised subject. The other 13 subjects were enrolled at a disqualified site. Data from Dr. Feicht's site were disqualified because they could not be reconciled against source documents; these data were excluded from the efficacy analyses. However, the efficacy results from Dr. Feicht's site were assessed. All 13 subjects were assigned a clinical response of cure by Dr. Feicht. Pretreatment pathogens included one *S. pneumoniae*, one *M. catarrhalis*, two *H. parainfluenzae*, and one *S. aureus* isolates; bacteriological responses for all these pathogens were cure. Therefore, if data from Dr. Feicht's site were included in the intent-to-treat analyses, the clinical cure rate, subject bacteriological cure rate, and overall pathogen eradication rate would have increased.

The number of subjects included in the efficacy analyses is presented by data set in the table below:

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Disposition of Subjects by Data Set		
	<u>Clarithromycin</u> <u>ER</u>	<u>Clarithromycin</u> <u>IR</u>
Total Randomized	320	307
Total Took Study Medication (All Treated Subjects Population)	317	303
Intent-to-Treat Analyses	300	285
Excluded from the Intent-to-Treat Analyses	17	18
Selection criteria not met	10	12
Disqualified investigator (12312) ^a	7	6
Clinically Evaluable Analyses	261	259
Excluded from the Clinically Evaluable Analyses	56	44
Selection criteria not met (all reasons; specific reasons listed below)	22	18
Subject did not return for Test-of-Cure Visit	11	10
Used confounding medication	12	5
Disqualified investigator (12312) ^a	7	6
Subject noncompliance with treatment regimen	4	3
Mistiming of Test-of-Cure Visit	0	2
Clinically and Bacteriologically Evaluable Analyses	100	82
Excluded from the Clinically and Bacteriologically Evaluable Analyses ^b	217	221
No target pathogen isolated pretreatment	181	193
Selection criteria not met (all reasons)	22	18
(Selection criteria not met: significant high pretreatment lab value)	(12)	(5)
(Selection criteria not met: no clinical diagnosis of AEBC)	(5)	(9)
(Selection criteria not met: pneumonia/positive chest x-ray)	(4)	(3)
(Selection criteria not met: immunocompromised)	(1)	(0)
(Selection criteria not met: took systemic antibiotics at pretreatment)	(0)	(1)
Disqualified investigator (12312) ^a	7	6
Did not return for Test-of-Cure Visit	3	3
Used confounding medication	3	1
Subject noncompliance with treatment regimen	1	0

a Efficacy data were disqualified because data could not be reconciled against source documents.

b If a subject is both bacteriologically and clinically nonevaluable, then the bacteriological nonevaluable reason is presented.

Demographics

There were no statistically significant differences between the treatment groups in sex, race, age, or weight. The majority of the subjects were female (56%) and white (87%). The mean age of all subjects was 54.4 years, and age ranged from 14 to 89 years. The table below presents the demographic information for all treated subjects.

Demographic Information (All Treated Subjects Population)			
Demographic Characteristic	Number of Subjects by Treatment Group		P-value ^a
	Clarithromycin ER	Clarithromycin IR	
Total Treated	317	303	
<u>Sex</u>			0.747
Female	181 (57%)	169 (56%)	
Male	136 (43%)	134 (44%)	
<u>Race^b</u>			0.812
White	277 (87%)	262 (86%)	
Black	18 (6%)	16 (5%)	
Asian	8 (3%)	12 (4%)	
Other	14 (4%)	13 (4%)	
<u>Age (years)</u>			0.829
<40	66 (21%)	65 (21%)	
40-64	161 (51%)	139 (46%)	
≥65	90 (28%)	99 (33%)	
Mean (SD)	54.3 (15.9)	54.6 (17.2)	
Range	14 - 86	16 - 89	
<u>Weight (kg)</u>			0.985
<45	3 (1%)	3 (1%)	
45 - <70	98 (31%)	90 (30%)	
≥70	211 (67%)	208 (69%)	
No data	5 (2%)	2 (1%)	
Mean (SD)	82.1 (22.4)	82.1 (21.0)	
Range	42 - 195	44 - 158	
a	P-values are from Fisher's exact test comparing treatment groups (sex, race), or a one-way analysis of variance model comparing treatment groups (age, weight).		
b	Race comparison was done with respect to two categories: white and all other races combined.		

Presenting Conditions, Medical History, and Diagnoses

The table below summarizes the presenting conditions, medical history, and social history for all treated subjects. A statistically significant difference was observed between treatment groups in the mean number of episodes of AECB within the past 12 months (p=0.048); higher percentages of subjects in the clarithromycin ER group than in the clarithromycin IR group had one or two prior episodes of AECB and a lower percentage had three or more episodes. This difference was not expected to affect the outcome of the study.

Summary of Presenting Conditions, Medical History, and Social History (All Treated Subjects Population)					
	Number of Subjects by Treatment Group				P-value ^a
	Clarithromycin ER 317		Clarithromycin IR 303		
Total Treated					
<u>Diseases/Conditions Present^b</u>					Not computed
Respiratory Disease	315	(99%)	299	(99%)	
Surgical History	287	(91%)	247	(82%)	
Musculoskeletal	177	(56%)	163	(54%)	
Eyes-Ears-Nose-Throat	164	(52%)	141	(47%)	
Cardiovascular	147	(46%)	151	(50%)	
Gastrointestinal	155	(49%)	134	(44%)	
Drug Allergy	129	(41%)	118	(39%)	
Non-Drug Allergy	112	(35%)	103	(34%)	
Neurologic	106	(33%)	101	(33%)	
Endocrine Disorder	78	(25%)	74	(24%)	
Cancer	40	(13%)	35	(12%)	
Renal Disease	43	(14%)	26	(9%)	
Occup./Environmental Hazard Exposure	25	(8%)	25	(8%)	
Drug/Alcohol Abuse	24	(8%)	9	(3%)	
Hepatic Disease	14	(4%)	14	(5%)	
<u>Pulmonary Disease^b</u>					Not computed
Acute Exacerbation of Chronic Bronchitis	314	(99%)	297	(98%)	
Chronic Bronchitis	314	(99%)	297	(98%)	
Community-Acquired Pneumonia	108	(34%)	94	(31%)	
Bronchial Asthma	101	(32%)	97	(32%)	
Tobacco Use					>0.999
Non-Tobacco User	73	(23%)	70	(23%)	
Ex-Tobacco User	106	(33%)	103	(34%)	
Tobacco User	138	(44%)	130	(43%)	
Overall Clinical Condition					0.729
Excellent	13	(4%)	17	(6%)	
Good	168	(53%)	148	(49%)	
Fair	115	(36%)	127	(42%)	
Poor	21	(7%)	11	(4%)	
Number of AECB in Past 12 Months					0.048*
1	55	(17%)	46	(15%)	
2	94	(30%)	80	(26%)	
≥3	168	(53%)	176	(58%)	
No Data	0	(0%)	1	(<1%)	
Mean (SD)	2.9	(1.6)	3.2	(2.0)	
Range					

* Indicates statistical significance at the 0.05 level.
a P-values are from Fisher's exact test for tobacco use, from Cochran-Mantel-Haenszel for overall clinical condition, and from ANOVA for number of AECB within past 12 months.
b Present in ≥5% of subjects in either treatment group.

Pretreatment Signs and Symptoms

No statistically significant differences were observed between the treatment groups in pre-acute signs and symptoms in any subject population. Prior to the current episode of AECB, the majority of subjects experienced mild cough (80%), mild sputum production

(75%), and produced less than one ounce of sputum daily (65%); 50% experienced dyspnea of mild, moderate or severe intensity. The table below presents the pre-acute signs and symptoms of all treated subjects.

Summary of Pre-Acute Signs and Symptoms (All Treated Subjects Population)					
	Number of Subjects by Treatment Group				P-value ^a
	Clarithromycin ER 317 ^b		Clarithromycin IR 303 ^b		
Total Treated					
Cough					0.357
Absent	12	(4%)	17	(6%)	
Mild	252	(79%)	243	(80%)	
Moderate	50	(16%)	37	(12%)	
Severe	1	(<1%)	4	(1%)	
Sputum Production					0.929
Absent	35	(11%)	43	(14%)	
Mild	249	(79%)	219	(72%)	
Moderate	29	(9%)	38	(13%)	
Severe	2	(1%)	1	(<1%)	
Sputum Production Volume					0.739
< 1 ounce	202	(64%)	199	(66%)	
1 - 2 ounces	91	(29%)	80	(26%)	
2 - 3 ounces	14	(4%)	15	(5%)	
> 3 ounces	8	(3%)	7	(2%)	
Dyspnea					0.872
Absent	161	(51%)	146	(48%)	
Mild	121	(38%)	134	(44%)	
Moderate	31	(10%)	19	(6%)	
Severe	2	(1%)	2	(1%)	
Fever					0.306
Absent	315	(99%)	300	(99%)	
Present	0	(0%)	1	(<1%)	

a P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.
 b No pre-acute signs and symptoms data were available for two subjects in each treatment group.

For acute pretreatment signs and symptoms, all subjects had cough and all but two subjects had purulent sputum at pretreatment (one additional subject had no data). Other frequently reported signs and symptoms at pretreatment for both groups combined included rhonchi/wheezing (77% of subjects), dyspnea (74%), and hoarseness (57%). Statistically significant differences were observed between the treatment groups in

sputum production ($p=0.042$) and headache ($p=0.019$); higher percentages of subjects in the clarithromycin ER group reported headache (45% versus 36%) and moderate or severe sputum production (86% versus 81%). The table below presents the pretreatment signs and symptoms of all treated subjects.

Summary of Current Acute Episode Pretreatment Clinical Signs and Symptoms (All Treated Subjects Population)					
	Number of Subjects by Treatment Group				P-value ^a
	Clarithromycin ER 317 ^b		Clarithromycin IR 303		
Total Treated					
<u>Cough</u>					0.108
Mild-	26	(8%)	34	(11%)	
Moderate	202	(64%)	198	(65%)	
Severe	88	(28%)	71	(23%)	
<u>Sputum Production</u>					0.042*
Absent	0	(0%)	1	(<1%)	
Mild	44	(14%)	57	(19%)	
Moderate	221	(70%)	207	(68%)	
Severe	51	(16%)	38	(13%)	
<u>Sputum Production (Volume)</u>					0.828
< 1 ounce	44	(14%)	43	(14%)	
1 - 2 ounces	135	(43%)	132	(44%)	
2 - 3 ounces	99	(31%)	92	(30%)	
> 3 ounces	38	(12%)	36	(12%)	
<u>Sputum Appearance</u>					0.976
Purulent Present	315	(99%)	302	(>99%)	
Purulent Absent	1	(<1%)	1	(<1%)	
<u>Sputum Appearance</u>					0.821
Blood Absent	298	(94%)	287	(95%)	
Blood Present	18	(6%)	16	(5%)	
<u>Dyspnea</u>					0.510
Absent	79	(25%)	81	(27%)	
Mild	108	(34%)	110	(36%)	
Moderate	112	(35%)	93	(31%)	
Severe	17	(5%)	19	(6%)	
<u>Rales/Crackling</u>					0.896
Absent	250	(79%)	241	(80%)	
Present	66	(21%)	62	(20%)	
<u>Egophony</u>					0.416
Absent	304	(96%)	295	(97%)	
Present	12	(4%)	8	(3%)	
<u>Rigors</u>					0.949
Absent	300	(95%)	288	(95%)	
Present	16	(5%)	15	(5%)	
<u>Rhonchi/Wheezing</u>					0.841
Absent	72	(23%)	67	(22%)	
Present	244	(77%)	236	(78%)	

Summary of Current Acute Episode Pretreatment Clinical Signs and Symptoms (All Treated Subjects Population) (Continued)					
	Number of Subjects by Treatment Group				P-value^a
	<u>Clarithromycin ER</u>		<u>Clarithromycin IR</u>		
<u>Substernal Pain</u>					0.974
Absent	251	(79%)	241	(80%)	
Present	65	(21%)	62	(20%)	
<u>Pleuritic Pain</u>					0.659
Absent	277	(87%)	262	(86%)	
Present	39	(12%)	41	(14%)	
<u>Pleural Effusion</u>					Not computed
Absent	316	(100%)	303	(100%)	
Present	0	(0%)	0	(0%)	
<u>Fever</u>					0.669
Absent	306	(97%)	296	(98%)	
Present	9	(3%)	7	(2%)	
<u>Headache</u>					0.019*
Absent	173	(55%)	194	(64%)	
Present	143	(45%)	109	(36%)	
<u>Coryza</u>					0.648
Absent	182	(57%)	180	(59%)	
Present	134	(42%)	123	(41%)	
<u>Hoarseness</u>					0.067
Absent	123	(39%)	140	(46%)	
Present	193	(61%)	163	(54%)	
<u>Sore Throat</u>					0.974
Absent	185	(58%)	177	(58%)	
Present	131	(41%)	126	(42%)	

* Indicates statistical significance at the 0.05 level.
 a P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.
 b No pretreatment signs and symptoms data were available for one subject in clarithromycin ER group; no fever data were available for two subjects in clarithromycin ER group.

Among intent-to-treat subjects, statistically significant differences were observed between treatment groups in pretreatment sputum production, headache, and hoarseness. Of the subjects in the clarithromycin ER and clarithromycin IR groups, moderate or severe sputum production was reported by 86% and 81%, respectively (p=0.044); headache was reported by 45% and 36%, respectively (p=0.021); and hoarseness was reported by 61% and 54%, respectively (p=0.046). Among clinically evaluable subjects, a statistically significant difference was observed between treatment groups in

pretreatment headache ($p=0.017$), with 45% of the clarithromycin ER and 35% of the clarithromycin IR group reporting this symptom. None of these differences were expected to affect the outcome of the study.

Concurrent Medications

Use of medications at pretreatment was similar between the treatment groups for the all treated subjects population; 90% of subjects in the clarithromycin ER group and 87% of the subjects in the clarithromycin IR group were taking medications at pretreatment. Overall, the most frequently used therapeutic classifications of medication at pretreatment were sympathomimetic agents (49%), nonsteroidal anti-inflammatory agents (25%), and analgesics, antipyretics, and anti-inflammatory agents (23%).

At pretreatment and prior to study drug administration, 21% of the subjects in each clarithromycin group were using medications to treat acute bronchitis. Overall, the most frequently used acute bronchitis medications at pretreatment were sympathomimetic agents (10%); antitussives (7%); expectorants (7%); and analgesics, antipyretics, and anti-inflammatory agents (6%).

During the study, 92% of the subjects in the clarithromycin ER group and 90% of the subjects in the clarithromycin IR group used concurrent medications. The majority of concurrent medications were used for treatment of coughs, colds, fevers, and other symptoms associated with bronchitis. Overall, 52% of all subjects used sympathomimetic agents; 27% used nonsteroidal anti-inflammatory agents; 24% used analgesics, antipyretics, and anti-inflammatory agents; 18% used vasodilating agents; 17% used H₁-receptor antagonists; 13% used anti-inflammatory (skin and mucous membrane) agents; 12% used expectorants; and 9% used antitussives during the study. In addition, 22% of subjects used adrenal corticosteroids (primarily inhaled agents); 15% used estrogens, and 15% used antidepressants. The most frequently used specific medications included albuterol (38% of subjects), acetaminophen (20%), ipratropium (18%), acetylsalicylic acid (15%), fluticasone (12%), salmeterol (12%), and guaifenesin (11%). The percentages of subjects in the clarithromycin ER and clarithromycin IR groups who used the above drugs were similar.

Four subjects (three clarithromycin ER and one clarithromycin IR) were excluded from the bacteriologically and clinically evaluable analyses because they took medications that could affect the outcome of the study. Seventeen subjects (12 clarithromycin ER and five clarithromycin IR) were excluded from the clinically evaluable analyses because they took confounding medications prior to the Test-of-Cure Visit. All of the subjects who were clinically nonevaluable were also clinically and bacteriologically nonevaluable; however, in the clinically and bacteriologically evaluable data set, bacteriological reasons for nonevaluability (e.g., no target pathogen) were listed above clinical reasons (e.g., confounding medication). All 13 additional subjects who were clinically nonevaluable due to confounding medications had no target pathogen isolated pretreatment. Details of the 17 subjects excluded from the clinically evaluable efficacy analyses due to confounding medications are presented in the table below:

Subjects Excluded From Clinically Evaluable Efficacy Analyses Due to Confounding Medications			
Investigator/ Subject Number	Confounding Medication	Study Day (days posttreatment)	Indication
Subjects Excluded From Clarithromycin ER Group			
Allen/4129	Biaxin®	9 (2)	Chronic bronchitis
Cutler/3686 ^a	Keflex®	14 (6)	Sinusitis
Dewan/4146# ^a	prednisone (>10 mg/day)	10 (3)	AECB
Hegewald/3789 ^a	prednisone (>10 mg/day)	16 (9)	Worsened asthma
Mansfield/3123	Cefin®	16 (9)	Acute sinusitis
Miller/3172 ^a	tetracycline HCl	12 (5)	<i>H. pylori</i>
Morowitz/3714# ^a	prednisone (>10 mg/day)	9 (2)	COPD, lower respiratory infection
Ondrejicka/3382 ^a	Bicillin C-R® (IM)	17 (10)	Sore throat & swollen glands
	Cefzil®	17 (10)	Sore throat & swollen glands
Safdi/3735 ^a	prednisone (>10 mg/day)	14 (7)	Acute exacerbation of asthma
Scott/3765	prednisone (>10 mg/day)	14 (7)	Bronchitis
Singh/3918 ^a	Deltasone® (>10 mg/day)	8 (1)	Bronchial inflammation
Singh/3923# ^a	Bactrim DS®	9 (1)	Otitis media; sinusitis
Subjects Excluded From Clarithromycin IR Group			
Dewan/4160	prednisone (>10 mg/day)	20 (13)	Chest tightness
Dotson/3986# ^a	cephalexin	8	Toe infection
Krause/4024 ^a	prednisone (>10 mg/day)	17 (10)	Pleurisy
McCarty/5107 ^a	Deltasone® (>10 mg/day)	10 (3)	Dyspnea
Siami/3981 ^a	Septra DS®	15 (7)	Urinary tract infection
# Subject prematurely discontinued from study.			
a Bacteriologically nonevaluable: no target pathogen isolated pretreatment.			

Measurement of Treatment Compliance

In the clinically and bacteriologically evaluable population, all subjects (100%) in the clarithromycin ER group and 95% of the subjects in the clarithromycin IR group were at least 80% compliant with the treatment regimen. This was reflected in a statistically significant difference in mean compliance ($p=0.009$). Duration of treatment and study drug compliance for clinically and bacteriologically evaluable subjects are presented in the table below:

Duration of Treatment and Study Drug Compliance (Clinically and Bacteriologically Evaluable Population)			
	<u>Clarithromycin ER</u>	<u>Clarithromycin IR</u>	<u>P-value^a</u>
Total Treated	100	82	
<u>Duration of Treatment (Days)</u>			0.113
<3	0 (0%)	1 (1%)	
3 - <5	0 (0%)	1 (1%)	
5 - <7	0 (0%)	1 (1%)	
≥7	100 (100%)	79 (96%)	
Mean (SD)	7.0 (0.20)	7.2 (1.03)	
Min - Max	7 - 8	2 - 12	
<u>Compliance (percentage)^b</u>			0.009*
20 - <80	0 (0%)	4 (5%)	
≥80	100 (100%)	78 (95%)	
Mean (SD)	100 (0.00)	97.1 (10.93)	
Min - Max	100 - 100	28.6 - 100	
* Indicates statistical significance at the 0.05 level.			
a P-value for F-test testing equality of treatment means.			
b Subjects who did not return study drug containers but reported full compliance were assumed 100% compliant.			

The mean duration of treatment was slightly higher in the clarithromycin IR group than in the clarithromycin ER group, with statistically significant differences for clinically evaluable subjects (p=0.008), intent-to-treat subjects (p=0.004), and all treated subjects (p=0.005). Compliance was high in all populations; ≥92% of subjects in the clarithromycin ER group and ≥94% of subjects in the clarithromycin IR group reported at least 80% compliance with the treatment regimen.

Efficacy Results and Tabulations of Individual Subject Data

Analysis of Efficacy

Bacteriological response was evaluated in subjects who were both bacteriologically and clinically evaluable and in intent-to-treat subjects with at least one target pathogen at pretreatment. Clinical response was evaluated in bacteriologically and clinically

evaluable subjects, clinically evaluable subjects, and intent-to-treat subjects. The test-of-cure assessment was made at Evaluation 3 (7 to 23 days posttreatment).

Primary Efficacy Variables

Subject Bacteriological Cure Rates

Among subjects who were both clinically and bacteriologically evaluable, 86% of the clarithromycin ER group and 85% of the clarithromycin IR group were classified as bacteriological cures at the Test-of-Cure Visit. The 95% confidence interval (CI) for the difference between subject bacteriological cure rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. Subject bacteriological cure rates and corresponding confidence intervals for clinically and bacteriologically evaluable subjects are presented in the table below:

Subject Bacteriological Cure Rates at the Test-of-Cure Visit (Clinically and Bacteriologically Evaluable Population)			
	<u>Clarithromycin ER</u>	<u>Clarithromycin IR</u>	
	n/N (%) [95% CI] ^b	n/N (%) [95% CI] ^b	P-value ^a [95% CI] ^c
Bacteriological Cure Rate ^d	85/99 ⁺ (86%) [77.4, 92.0]	70/82 (85%) [75.8, 92.2]	>0.999 [-9.8, 10.8]
<p>⁺ One subject with indeterminate bacteriologic response was not included in calculating the rate.</p> <p>^a P-value is from Fisher's exact test comparing treatment groups.</p> <p>^b Exact binomial confidence interval.</p> <p>^c Binomial confidence interval based on normal approximation.</p> <p>^d Assessment was made at Evaluation 3 (7 to 23 days posttreatment) unless the subject was a bacteriological failure before Evaluation 3.</p>			

Subject bacteriological responses at the Test-of-Cure Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for country, investigator, sex, race, age, weight, overall clinical condition, number of AECB within past 12 months, study drug duration, study drug compliance, and tobacco use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups. Results in intent-to-treat subjects were similar to those in clinically and bacteriologically evaluable subjects. Subject bacteriological cure rates at the Test-of-Cure Visit were 76% (85/112) in the clarithromycin ER group and 80% (70/88) in the clarithromycin IR group. The drop in bacteriologic cure rate from clinically and bacteriologically evaluable subjects to intent-to-treat subjects is mainly due to the fact that subjects with indeterminate bacteriologic responses were treated as bacteriological failures in the intent-to-treat analysis. The 95% CI for the difference in cure rates demonstrated that the two treatments were equivalent. No statistically significant treatment differences were observed after adjusting for a variety of potentially influential factors.

Pathogen Eradication Rates

Among subjects who were both clinically and bacteriologically evaluable, no statistically significant differences were observed between treatment groups in overall pathogen eradication rates at the Test-of-Cure Visit. The 95% confidence interval (CI) for the difference between overall eradication rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. Eradication rates for the target pathogens were similar in the two treatment groups. Overall eradication rates and corresponding confidence intervals, as well as target pathogen eradication rates, for clinically and bacteriologically evaluable subjects are presented in the table below.

Target Pathogen Eradication Rates at the Test-of-Cure Visit (Clinically and Bacteriologically Evaluable Population)				
	<u>Clarithromycin ER</u> n/N (%) [95% CI] ^b	<u>Clarithromycin IR</u> n/N (%) [95% CI] ^b	<u>P-value^a</u> [95% CI] ^c	
Overall Pathogen Eradication Rate ^d	100/116 (86%) [78.6, 91.9]	86/98 (88%) [79.6, 93.5]	0.840 [-10.6, 7.5]	
Eradication Rate ^d				
<i>H. influenzae</i>	22/28 (79%)	17/22 (77%)	>0.999	
<i>M. catarrhalis</i>	22/25 ⁺ (88%)	25/26 ⁺ (96%)	0.350	
<i>S. pneumoniae</i>	22/25 (88%)	9/11 (82%)	0.631	
<i>H. parainfluenzae</i>	24/26 (92%)	25/28 (89%)	>0.999	
<i>S. aureus</i>	10/12 (83%)	10/11 (91%)	>0.999	
+ One subject had indeterminate bacteriological response and was not included in the calculation of eradication rates.				
a P-value is from Fisher's exact test comparing treatment groups.				
b Exact binomial confidence interval.				
c Binomial confidence interval based on normal approximation.				
d Assessment was made at Evaluation 3 (7-23 days posttreatment) unless the pathogen persisted (i.e., bacteriological failure) before Evaluation 3.				

MEDICAL OFFICER'S COMMENTS:

The applicant is requesting that the following statement be included in the INDICATIONS AND USAGE section of the label:

"Treatment of Acute bacterial exacerbation of chronic bronchitis due to Haemophilus parainfluenzae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, or Streptococcus pneumoniae."

The current package insert has the following statement:

“Treatment of Acute bacterial exacerbation of chronic bronchitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae.”

The applicant is requesting additions of two microorganisms – S. aureus and H. parainfluenzae for this particular indication.

Based upon the data submitted, and reanalyzed by this Medical Officer, the total number of H. parainfluenzae isolated in the clarithromycin ER arm were 26, and out of 26 isolates, 20 were pure cultures. The eradication rate was 19/20 (95%). In the clarithromycin IR arm, the numbers of isolates were 28, and out of those 28 isolates, 19 were pure cultures. The eradication rate in the IR arm was 17/19 (89%).

The total number of S. aureus isolated in the clarithromycin ER arm were 12, and out of 12 isolates, 8 were pure cultures. The eradication rate was 6/8 (75%). In the clarithromycin IR arm, the number of isolates were 11, and out of those 11 isolates, 6 were pure cultures. The eradication rate in the IR arm was 5/6 (83%).

Results in intent-to-treat subjects were similar to those in clinically and bacteriologically evaluable subjects. Overall pathogen eradication rates at the Test-of-Cure Visit were 77% (100/130) in the clarithromycin ER group and 80% (86/107) in the clarithromycin IR group. The drop in bacteriological cure rate from clinically and bacteriologically evaluable subjects to intent-to-treat subjects is mainly due to the fact that subjects with indeterminate bacteriologic responses were treated as bacteriological failures in the intent-to-treat analyses. The 95% CI for the difference in overall pathogen eradication rates demonstrated that the two treatments were equivalent. No statistically significant differences were observed between the treatment groups in the eradication rates for the target pathogens.

Clinical Cure Rates

Subject Clinical Responses (Clinically and Bacteriologically Evaluable Subjects)

Among subjects who were both clinically and bacteriologically evaluable, 83% of subjects in the clarithromycin ER group and 82% of subjects in the clarithromycin IR group were classified as clinical cures at the Test-of-Cure Visit. The 95% confidence interval (CI) for the difference between clinical cure rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. Clinical cure rates and corresponding confidence intervals for clinically and bacteriologically evaluable subjects are presented in the table below:

Clinical Cure Rates at the Test-of-Cure Visit (Clinically and Bacteriologically Evaluable Population)			
	<u>Clarithromycin ER</u>	<u>Clarithromycin IR</u>	
	n/N (%) [95% CI] ^b	n/N (%) [95% CI] ^b	P-value ^a [95% CI] ^c
Clinical Cure Rate ^d	83/100 (83%) [74.2, 89.8]	67/82 (82%) [71.6, 89.4]	0.847 [-9.9, 12.4]
<p>a P-value is from Fisher's exact test comparing treatment groups.</p> <p>b Exact binomial confidence interval.</p> <p>c Binomial confidence interval based on normal approximation.</p> <p>d Assessment was made at Evaluation 3 (7-23 days posttreatment) unless the subject was a clinical failure before Evaluation 3.</p>			

Clinical responses at the Test-of-Cure Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for country, investigator, sex, race, age, weight, overall clinical condition, number of AECB within past 12 months, study drug duration, study drug compliance, and tobacco use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Subject Clinical Responses (Clinically Evaluable Subjects)

Among subjects who were clinically evaluable, 80% of subjects in the clarithromycin ER group and 83% of subjects in the clarithromycin IR group were classified as clinical cures at the Test-of-Cure Visit. The 95% confidence interval (CI) for the difference between clinical cure rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. Clinical cure rates and corresponding confidence intervals for clinically evaluable subjects are presented in the table below:

Clinical Cure Rates at the Test-of-Cure Visit (Clinically Evaluable Population)			
	<u>Clarithromycin ER</u>	<u>Clarithromycin IR</u>	
	n/N (%) [95% CI] ^b	n/N (%) [95% CI] ^b	P-value ^a [95% CI] ^c
Clinical Cure Rate ^d	209/261 (80%) [74.7, 84.7]	214/25 (83%) 9 [77.5, 87.0]	0.500 [-9.2, 4.1]
<p>a P-value is from Fisher's exact test comparing treatment groups.</p> <p>b Exact binomial confidence interval.</p> <p>c Binomial confidence interval based on normal approximation.</p> <p>d Assessment was made at Evaluation 3 (7-23 days posttreatment) unless the subject was a clinical failure before Evaluation 3.</p>			

Clinical responses at the Test-of-Cure Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for country, investigator, sex, race, age, weight, overall clinical condition, number of AECB within past 12 months, study drug duration, study drug compliance, and tobacco use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Results in intent-to-treat subjects were similar to those in clinically evaluable subjects. Clinical cure rates at the Test-of-Cure Visit were 70% (211/300) in the clarithromycin ER group and 75% (215/285) in the clarithromycin IR group. The drop in clinical cure rate from clinically and bacteriologically evaluable subjects to intent-to-treat subjects is mainly due to the fact that subjects with indeterminate clinical responses were treated as clinical failures in the intent-to-treat analyses. The 95% CI for the difference in clinical cure rates demonstrated that the two treatments were equivalent. No statistically significant treatment differences were observed after adjusting for potentially influential factors.

Secondary Efficacy Variable

Subject Clinical Response for Target Pathogens

Among clinically and bacteriologically evaluable subjects, no statistically significant differences were observed between the treatment groups in clinical cure rates for subjects who had the target pathogens. Subject clinical cure rates for target pathogens for clinically and bacteriologically evaluable subjects are presented in the table below:

Subject Clinical Cure Rates for Target Pathogens (Clinically and Bacteriologically Evaluable Population)					
Target Pathogen ^b	Clarithromycin ER n/N (%)		Clarithromycin IR n/N (%)		P-value ^a
	<i>H. influenzae</i>	21/28	(75%)	17/22	
<i>M. catarrhalis</i>	22/26 ⁺	(85%)	22/27 ⁺	(81%)	>0.999
<i>S. pneumoniae</i>	21/25	(84%)	8/11	(73%)	0.650
<i>H. parainfluenzae</i>	24/26	(92%)	25/28	(89%)	>0.999
<i>S. aureus</i>	10/12	(83%)	10/11	(91%)	>0.999

+ One subject had indeterminate bacteriological response and was not included in the calculation of eradication rates.

a P-values are from Fisher's exact test comparing treatment groups.

b Assessment was made at Evaluation 3 (7-23 days posttreatment) unless the subject was a clinical failure before Evaluation 3.

Results among intent-to-treat subjects were generally similar to those among clinically and bacteriologically evaluable subjects, with no statistically significant treatment differences.

Bacteriological Response versus Clinical Response

The subject bacteriologic responses were compared with subject clinical responses in both treatment groups at the Test-of-Cure Visit. Differences occurred in two subjects in the clarithromycin ER group and five subjects in the clarithromycin IR group. Two subjects in the clarithromycin ER group and four subjects in the clarithromycin IR who were bacteriological cures had a clinical response of failure; in addition, one subject in the clarithromycin IR group who was a bacteriological failure had a clinical response of cure.

Results in intent-to-treat subjects were similar to those in clinically and bacteriologically evaluable subjects. These results demonstrate the general correlation of clinical improvement and bacteriological eradication.

Resolution/Improvement of Pretreatment Signs and Symptoms at Evaluation 2

In clinically and bacteriologically evaluable subjects, there were no statistically significant differences between treatment groups at Evaluation 2 (0 to 5 days posttreatment) in the percentage of subjects showing resolution or resolution/improvement in cough, sputum production, sputum production volume, and dyspnea, or resolution in sputum appearance (purulent), sputum appearance (hemoptic), rales/crackling, egophony, rigors, rhonchi/wheezing, substernal pain, pleuritic pain, pleural effusion, fever, headache, coryza, hoarseness, and sore throat.

A summary of the resolution and resolution/improvement rates for all signs and symptoms at Evaluation 2 is presented in the table below for clinically and bacteriologically evaluable subjects.

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Resolution and/or Improvement of Pretreatment Signs/Symptoms at Evaluation 2 (Clinically and Bacteriologically Evaluable Population)					
Sign/Symptom ^a	Clarithromycin ER		Clarithromycin IR		P-value ^b
<u>Cough</u>					
Resolution	14/96	(15%)	15/79	(19%)	0.541
Resolution/Improvement	75/96	(78%)	69/79	(87%)	0.163
<u>Sputum Production</u>					
Resolution	60/96	(63%)	48/79	(61%)	0.876
Resolution/Improvement	84/96	(88%)	69/79	(87%)	>0.999
<u>Sputum Production (Volume)</u>					
Resolution	59/83	(71%)	56/71	(79%)	0.353
Resolution/Improvement	71/83	(86%)	68/71	(96%)	0.054
<u>Sputum Appearance (Purulent)</u>					
Resolution	73/96	(76%)	66/79	(84%)	0.262
<u>Sputum Appearance (Hemoptic)</u>					
Resolution	7/7	(100%)	7/7	(100%)	N/A
<u>Dyspnea</u>					
Resolution	35/74	(47%)	25/56	(45%)	0.859
Resolution/Improvement	56/74	(76%)	41/56	(73%)	0.839
<u>Rales/Crackling</u>					
Resolution	14/20	(70%)	11/16	(69%)	>0.999
<u>Egophony</u>					
Resolution	4/5	(80%)	2/2	(100%)	>0.999
<u>Rigors</u>					
Resolution	5/5	(100%)	3/3	(100%)	N/A
<u>Rhonchi/Wheezing</u>					
Resolution	45/72	(63%)	41/57	(72%)	0.347
<u>Substernal Pain</u>					
Resolution	21/22	(95%)	14/18	(78%)	0.155
<u>Pleuritic Pain</u>					
Resolution	12/12	(100%)	9/10	(90%)	0.455
<u>Pleural Effusion</u>					
Resolution	0/0		0/0		N/A
<u>Fever</u>					
Resolution	3/3	(100%)	2/2	(100%)	N/A
<u>Headache</u>					
Resolution	31/37	(84%)	22/30	(73%)	0.370
<u>Coryza</u>					
Resolution	34/48	(71%)	23/31	(74%)	0.802
<u>Hoarseness</u>					
Resolution	41/58	(71%)	31/43	(72%)	>0.999
<u>Sore Throat</u>					
Resolution	38/42	(90%)	25/30	(83%)	0.476

N/A = not applicable
 a Pretreatment assessment was made on or before Study Day 1; Evaluation 2 assessment was made 0-5 days posttreatment.
 b P-values are from Fisher's exact test comparing treatment groups.

Resolution/Improvement of Pretreatment Signs and Symptoms at Evaluation 3

In clinically and bacteriologically evaluable subjects, there were no statistically significant differences between treatment groups at Evaluation 3 (7 to 23 days posttreatment) in the percentage of subjects showing resolution or resolution/improvement in cough, sputum production, sputum production volume, and

dyspnea, or resolution in sputum appearance (hemoptic), rales/crackling, egophony, rigors, rhonchi/wheezing, substernal pain, pleuritic pain, pleural effusion, fever, headache, coryza, hoarseness, and sore throat. A significant treatment difference was observed in sputum appearance (purulent), with a higher percentage of subjects in the clarithromycin ER group (96%) than in the clarithromycin IR group (85%) showing resolution of this symptom. A summary of the resolution and resolution/improvement rates for all signs and symptoms at Evaluation 3 is presented in the table below for clinically and bacteriologically evaluable subjects.

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Resolution and/or Improvement of Pretreatment Signs/Symptoms at Evaluation 3 (Clinically and Bacteriologically Evaluable Population)					
Sign/Symptom ^a	Clarithromycin ER		Clarithromycin IR		P-value ^b
<u>Cough</u>					
Resolution	26/93	(28%)	25/75	(33%)	0.501
Resolution/Improvement	80/93	(86%)	70/75	(93%)	0.142
<u>Sputum Production</u>					
Resolution	67/93	(72%)	52/75	(69%)	0.735
Resolution/Improvement	90/93	(97%)	67/75	(89%)	0.064
<u>Sputum Production (Volume)</u>					
Resolution	71/81	(88%)	57/68	(84%)	0.637
Resolution/Improvement	79/81	(98%)	63/68	(93%)	0.247
<u>Sputum Appearance (Purulent)</u>					
Resolution	89/93	(96%)	64/75	(85%)	0.028*
<u>Sputum Appearance (Hemoptic)</u>					
Resolution	7/7	(100%)	7/7	(100%)	N/A
<u>Dyspnea</u>					
Resolution	37/73	(51%)	34/53	(64%)	0.149
Resolution/Improvement	55/73	(75%)	45/53	(85%)	0.265
<u>Rales/Crackling</u>					
Resolution	16/20	(80%)	15/17	(88%)	0.667
<u>Egophony</u>					
Resolution	3/4	(75%)	2/2	(100%)	>0.999
<u>Rigors</u>					
Resolution	5/5	(100%)	3/3	(100%)	N/A
<u>Rhonchi/Wheezing</u>					
Resolution	57/70	(81%)	44/54	(81%)	>0.999
<u>Substernal Pain</u>					
Resolution	20/22	(91%)	16/18	(89%)	>0.999
<u>Pleuritic Pain</u>					
Resolution	11/12	(92%)	10/11	(91%)	>0.999
<u>Pleural Effusion</u>					
Resolution	0/0		0/0		N/A
<u>Fever</u>					
Resolution	3/3	(100%)	2/2	(100%)	N/A
<u>Headache</u>					
Resolution	31/38	(82%)	25/28	(89%)	0.498
<u>Coryza</u>					
Resolution	34/46	(74%)	26/29	(90%)	0.140
<u>Hoarseness</u>					
Resolution	42/57	(74%)	32/40	(80%)	0.628
<u>Sore Throat</u>					
Resolution	37/43	(86%)	24/29	(83%)	0.747

N/A = not applicable
 * Indicates statistical significance at the 0.05 level.
 a Pretreatment assessment was made on or before Study Day 1; Evaluation 3 assessment was made 7-23 days posttreatment.
 b P-values are from Fisher's exact test comparing treatment groups.

Among clinically evaluable subjects at Evaluation 3, a significant treatment difference was observed in coryza, with a higher percentage of subjects in the clarithromycin IR group (84%) than in the clarithromycin ER group (70%) showing resolution of this

symptom (p=0.030). Results were similar among intent-to-treat subjects at Evaluation 3, with 84% of subjects in the clarithromycin IR group and 71% of subjects in the clarithromycin ER group showing resolution of coryza (p=0.046).

Applicant's Efficacy Conclusions

At the Test-of-Cure Visit, no statistically significant differences were observed between the treatment groups in subject bacteriological cure rates, overall pathogen eradication rates, and clinical cure rates. The 95% CI demonstrated that the two treatment regimens were equivalent. Clinical signs and symptoms of AECB resolved in subjects treated with either regimen.

Results of this study indicate that clarithromycin ER (2 x 500 mg QD for 7 days) was equivalent to clarithromycin IR (500 mg BID for 7 days) in treating acute exacerbation of chronic bronchitis due to *Haemophilus parainfluenzae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Streptococcus pneumoniae* in adult subjects.

Safety Evaluations

All subjects who received at least one dose of study drug (N=620) were included in the safety analyses (all treated subjects population).

Extent of Exposure

Ninety-three percent (93%) of the 317 subjects assigned to clarithromycin ER and 95% of the 303 subjects assigned to clarithromycin IR completed at least 7 days of the 7-day treatment regimen. A summary of the extent of exposure to study drug is presented by treatment group in the table below:

Extent of Exposure (All Treated Subjects Population)		
	Clarithromycin ER	Clarithromycin IR
Total Treated	317	303
<u>Duration of Treatment (Days)</u>		
<3	8 (3%)	6 (2%)
3 - <5	9 (3%)	4 (1%)
5 - <7	6 (2%)	6 (2%)
≥7	292 (93%)	284 (95%)
Missing	2	3
Mean (SD)	6.8 (1.17)	7.0 (1.09)
Min - Max	1 - 10	1 - 12

Brief Summary of Adverse Events

The incidence of all treatment-emergent adverse events was 39% in the clarithromycin ER group and 31% in the clarithromycin IR group. Excluding events judged not related or probably not related to study drug, one or more adverse events were reported by 22% of the clarithromycin ER group and 17% of clarithromycin IR group. The most frequently occurring study drug-related adverse events in both treatment groups were diarrhea, taste perversion, and nausea.

One subject who had been assigned to clarithromycin ER died more than 30 days after the last dose of study drug; the death (cardiopulmonary arrest) was considered not related to study drug. Twelve subjects (eight in the clarithromycin ER group and four in the clarithromycin IR group) had serious adverse events during the study, including one death, two subjects with adverse events requiring intervention only, and nine subjects who were hospitalized; all but one of the serious adverse events were considered not related or probably not related to study drug.

Eighteen subjects (nine in each group) were prematurely discontinued from treatment due to the occurrence of at least one adverse event. In the clarithromycin ER group, three subjects each discontinued treatment due to at least one adverse event associated with the digestive system and the body as a whole, two subjects discontinued for adverse events associated with the skin and appendages, and one subject discontinued for respiratory adverse events. In the clarithromycin IR group, six subjects discontinued treatment due to at least one adverse event associated with the digestive system, and one subject each discontinued due to adverse events associated with the skin and appendages, body as a whole, and cardiovascular body systems.

Of the 620 treated subjects who took study drug, 124 subjects (39%) in the clarithromycin ER group and 94 (31%) in the clarithromycin IR group reported at least one treatment-emergent adverse event. Overall, the most commonly reported adverse events in the clarithromycin ER and clarithromycin IR groups included diarrhea (8% and 5%, respectively), taste perversion (4% and 4%, respectively), and nausea (3% and 4%, respectively). Most adverse events in both treatment groups were considered mild or moderate in intensity. Eighteen (6%) subjects in the clarithromycin ER group reported 20 severe events (diarrhea and taste perversion by three subjects each, and asthenia, chest pain, headache, atrial flutter, cerebrovascular accident, heart arrest, gastroenteritis, flatulence, agitation, convulsion, asthma, bronchitis, hemoptysis, and respiratory disorder by one subject each). Fourteen (5%) subjects in the clarithromycin IR group reported 16 severe events (diarrhea by four subjects, headache by three subjects, and accidental injury, peripheral vascular disorder, dyspepsia, gastritis, gastroenteritis, nausea, dry mouth, flatulence, and tongue discoloration by one subject each).

A summary of all treatment-emergent adverse events reported by $\geq 3\%$ of subjects in either treatment group is presented by treatment group in the table below:

Summary of Common Treatment-Emergent Adverse Event Incidence Rates by COSTART Term (All Adverse Events)										
Adverse Events ^a	Clarithromycin ER (N=317) Severity ^b					Clarithromycin IR (N=303) Severity ^b				
	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Diarrhea	16	5	3	24	8%	8	4	4	16	5%
Taste perversion	8	2	3	13	4%	9	4	0	13	4%
Nausea	6	5	0	11	3%	4	6	1	11	4%
Headache	4	6	1	11	3%	5	2	3	10	3%

Mod = moderate; Sev = severe

a Adverse events occurring in $\geq 3\%$ of subjects in either treatment group.
 B Table summarizes the most severe occurrence of each COSTART term from each subject.

When events judged not related or probably not related to study drugs were excluded, 22% (70/317) of subjects in the clarithromycin ER group and 17% (52/303) of subjects in the clarithromycin IR group reported at least one adverse event considered possibly or probably related to study drug therapy. The most frequently occurring ($\geq 3\%$) study drug-related adverse events in the clarithromycin ER and clarithromycin IR groups were diarrhea (6% and 4%, respectively), taste perversion (4% and 4%, respectively), and nausea (3% and 3%, respectively). A summary of adverse events, excluding events judged not related or probably not related to study drugs, reported by $\geq 1\%$ (three or more) of subjects in either treatment group is presented by treatment group in the table below:

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Summary of Common Treatment-Emergent Adverse Event Incidence Rates by COSTART Term (Excluding Events Judged Not Related or Probably Not Related to Study Drugs)										
Adverse Events ^a	Clarithromycin ER (N=317) Severity ^b					Clarithromycin IR (N=303) Severity ^b				
	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Diarrhea	13	5	1	19	6%	6	3	3	12	4%
Taste perversion	8	2	3	13	4%	9	4	0	13	4%
Nausea	4	4	0	8	3%	4	4	1	9	3%
Oral moniliasis	3	3	0	6	2%	1	0	0	1	<1%
Gastritis	3	2	0	5	2%	0	1	1	2	<1%
Headache	1	4	0	5	2%	4	1	1	6	2%
Lab test abnormal	3	0	0	4 ^c	1%	1	1	0	2	<1%
Dyspepsia	0	0	0	0	0%	1	3	0	4	1%

Mod = moderate; Sev = severe

a Adverse events occurring in $\geq 1\%$ of subjects in either treatment group.

b Table summarizes the most severe occurrence of each COSTART term from each subject.

c Severity of one adverse event was unknown.

Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Investigator Cutler, Subject 3686, a 67-year-old white female who had been assigned to the clarithromycin ER group, experienced a cardiopulmonary arrest and died more than 30 days after the last day of study drug. The cardiopulmonary arrest was considered not related to study drug, with poor general health as the etiology.

Twelve subjects (eight in the clarithromycin ER group and four in the clarithromycin IR group) had serious adverse events. Only one serious adverse event (atrial flutter) was considered possibly related to study drug. Serious adverse events included one death, two events that required intervention only, and nine hospitalizations which included two events that required intervention and two events that were considered a permanent disability and also required intervention. Details concerning subjects who had serious adverse events are displayed by treatment group in the table below:

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Subjects Who Had Serious Adverse Events						
Investigator/ Subject Number	Age (yrs)/ Sex	Day of Onset ^a	Day of Resolution ^a	Body System	COSTART Term	Reason Serious
Subjects in the Clarithromycin ER Treatment Group with Serious Adverse Events						
Cutler/3686	67/F	44 (36)	44 (36)	Cardiovascular	Heart arrest	Death
Dewan/3959#	72/F	14 (7)	15 (8)	Cardiovascular	Cerebrovascular accident	HO
Dewan/4155	41/F	6	6	Nervous	Convulsion	HO
Dotson/3472	62/M	21 (13)	25 (17)	Respiratory	Hemoptysis	HO
Dotson/4231#	73/M	4 (1)	13 (10)	Respiratory	Bronchitis	HO
Feldstein/3429	64/M	15 (8)	17 (10)	Respiratory	Respiratory disorder	HO/PD/ RI
Safdi/3735	57/F	14 (7)	17 (10)	Respiratory	Asthma	RI
Spink/5067	63/M	8 (1)	Ongoing	Cardiovascular	Atrial flutter ^b	RI
Subjects in the Clarithromycin IR Treatment Group with Serious Adverse Events						
Feldstein/3430#	72/M	4	32 (25)	Cardiovascular	Peripheral vascular disorder	RI/HO
Fisher/3287#	53/F	3 (2)	5 (4)	Cardiovascular	Angina pectoris	HO
Nayak/3261#	83/M	3	5	Body as a whole	Chest pain	RI/HO
Rollins/3329	71/M	21 (14)	Ongoing	Body as a whole	Accidental injury	HO/PD/ RI
HO = hospitalization; RI = required intervention; PD = permanent disability						
# Subject prematurely discontinued the study.						
a Numbers in parentheses are days relative to last dose of study drug.						
b Drug-relationship classified as possible.						

Nine subjects in the clarithromycin ER group and nine subjects in the clarithromycin IR group were prematurely discontinued from treatment due to the occurrence of at least one adverse event, most of which were considered related to study drugs. Six of nine subjects in the clarithromycin IR group discontinued treatment due to at least one gastrointestinal adverse event, whereas three of nine subjects in the clarithromycin ER group discontinued due to at least one gastrointestinal adverse event. Details concerning subjects discontinued study drug due to adverse events are displayed by treatment group in the table below:

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Subjects Who Prematurely Discontinued Treatment Due to Adverse Events					
Investigator/ Subject Number	Age (yrs)/ Sex	Day of Onset ^a	Day of Resolution ^a	Body System	COSTART Term
Subjects Discontinued from the Clarithromycin ER Treatment Group					
Allen/4253	65/F	3	3	Body as a whole	Allergic reaction ^b
Dotson/4231	73/M	4 (1)	13 (10)	Respiratory	Bronchitis
Jannetti/3227	52/F	4	8 (2)	Skin and appendages	Rash ^b
Mansfield/3122	41/F	5	9 (3)	Body as a whole	Allergic reaction ^b
Miller/3170	70/F	5 (1)	40 (36)	Digestive	Colitis
Moriarty/3708	67/M	1	2 (1)	Digestive	Diarrhea ^b
		1	2 (1)	Digestive	Nausea ^b
Nayak/3268	73/F	5	6	Body as a whole	Abdomen enlarged ^b
Siami/4074	51/M	2	9 (6)	Skin and appendages	Urticaria ^b
Weinstein/3373	59/F	3	3	Digestive	Diarrhea
Subjects Discontinued from the Clarithromycin IR Treatment Group					
Cutler/3690	63/M	2	2	Body as a whole	Headache ^b
		2	2	Digestive	Diarrhea ^b
		2	2	Digestive	Nausea ^b
Fisher/3287	53/F	3 (2)	5 (4)	Cardiovascular	Angina pectoris
Gellrick/3306	54/F	5	10 (4)	Skin and appendages	Urticaria ^b
Hegewald/3790	72/M	2	6 (2)	Digestive	Gastroenteritis ^b
Kliner/3762	71/M	2	3 (1)	Digestive	Gastritis ^b
Miller/3931	76/M	3	7 (1)	Digestive	Nausea ^b
Moriarty/4197	69/M	1	2 (1)	Digestive	Nausea ^b
Munk/4071	49/F	2	4 (2)	Body as a whole	Headache ^b
Nayak/3267	57/F	2	3	Digestive	Diarrhea
		2	2	Digestive	Vomiting
a Numbers in parentheses are days relative to last dose of study drug.					
b Drug-relationship classified as possible or probable.					

Clinical Laboratory Evaluation

No subject in either treatment group had a hematology value which met the sponsor-defined criteria for possibly clinically significant. Four subjects in each treatment group had a serum chemistry value that met the sponsor-defined criteria for possibly clinically significant. A summary of these patients is presented in the table below:

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Subjects with Serum Chemistry Values That Met Sponsor-Defined Possibly Clinically Significant Criteria								
Subjects in the Clarithromycin ER Treatment Group								
Investigator/ Subject Number	Age (yrs)/ Sex	Variable	Baseline Value ^a	Study Day	Possibly Significant Value	Study Day	Final Value	CS Criteria
Bryya/3869	71/M							
Bryya/3992	79/M							
Feicht/3426	77/M							
Milgrom/3519	46/F							
Subjects in the Clarithromycin IR Treatment Group								
Brazinsky/4113	84/M							
Hartley/3234	72/F							
Moriarty/3704	82/M							
Rollins/4093	67/F							

Reference ranges: BUN = 4 - 24 mg/dL; creatinine = 0.5 - 1.2 (males) and 0.4 - 1.1 (females); SGPT/ALT = 6-43 (males) and 6-34 (females).
 H = above normal reference range; VH = very high (potentially clinically significant);
 CS = Clinically significant; ULN = Upper limit of normal; Base = Baseline value
^a Baseline is last value before study drug administration.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Minor increases and decreases from pretreatment in mean values for systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and weight were observed in both treatment groups, none of which were considered to be clinically meaningful.

Three subjects in the clarithromycin ER group and two subjects in the clarithromycin IR group had values for vital signs that met sponsor-defined possibly clinically significant criteria. Four subjects (three clarithromycin ER and one clarithromycin IR) had values for temperature that met potentially clinically significant decreases because they had fever at baseline; none of these changes in temperature were considered to be clinically meaningful.

The one remaining subject had a change in diastolic blood pressure. Investigator Dewan, Subject 4150 in the clarithromycin IR group had a baseline diastolic blood pressure of 73 mmHg that decreased to 40 mmHg on Day 9, two days after the last dose of study drug. This subject's final diastolic blood pressure on Day 21, 14 days after the last dose of study drug, was 81 mmHg. This change in diastolic blood pressure was asymptomatic and was considered by the investigator to be of no clinical concern.

Applicant's Safety Conclusions

No statistically significant differences were observed between the two groups in the incidence of adverse events excluding those judged not related or probably not related to study drug, although the incidence of all treatment-emergent adverse events was higher in the clarithromycin ER group. The most frequently occurring study drug-related adverse events in both treatment groups were diarrhea, taste perversion, and nausea.

Twelve serious adverse events (eight in the clarithromycin ER group and four in the clarithromycin IR group) were reported during the study. In the clarithromycin ER group, one subject died more than 30 days after the last dose of study drug, two subjects required intervention for adverse events, and five subjects were hospitalized for

conditions considered not related or probably not related to study drug. In the clarithromycin IR group, four subjects were hospitalized, three of whom also required intervention. Eighteen subjects (nine in each group) were prematurely discontinued from treatment due to the occurrence of at least one adverse event, most of which were considered related to study drug.

Changes in laboratory and vital signs were minor and were not considered clinically significant. Both clarithromycin ER and clarithromycin IR were safe and well tolerated.

Applicant's Overall Conclusions

Clarithromycin immediate release tablets and clarithromycin granules for oral suspension are indicated for the treatment of acute exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* in both adults and children. The new clarithromycin formulation for once a day dosing has been formulated to provide similar pharmacokinetics to the twice a day immediate release clarithromycin. The new clarithromycin extended release formulation is bioequivalent to the immediate release tablets given twice daily for AUC_{0-24} and C_{min} . Thus, the extended release clarithromycin should have equal efficacy when compared to the immediate release formulation given twice daily.

In this study, the two formulations were compared for bacteriological and clinical efficacy in the treatment of AECB and, as expected, there were no statistically significant differences in bacteriological response, overall pathogen eradication, or clinical response. At the Test-of-Cure Visit (Evaluation 3) in clinically and bacteriologically evaluable subjects, bacteriological cure rates were 86% in the clarithromycin ER group and 85% in the clarithromycin IR group. Overall pathogen eradication rates were 86% in the clarithromycin ER group and 88% in the clarithromycin IR group. Clinical cure rates were also similar for subjects who took clarithromycin ER (83%) and clarithromycin IR (82%). The 95% CI demonstrated that the two treatments were equivalent in bacteriological response, overall pathogen eradication, and clinical response.

The efficacy of clarithromycin treatment in the eradication of five target pathogens was examined: *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, and *S. aureus*. Three of the pathogens, *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*, were included for treatment by the current IR formulation; the remaining two pathogens were included in the approval for AECB in recent FDA filings (Trovan Package Insert, Levaquin Package Insert). *S. aureus* is the better recognized pathogen in AECB; *H. parainfluenzae* is somewhat less well recognized. This organism has been frequently isolated in significant quantities during acute exacerbations and was isolated as frequently as *H. influenzae* in the current clinical trial.

It should be noted that the primary endpoints for efficacy were redefined in the February 1997 Guidelines for Industry in which clinical cure replaced clinical success. In addition, the Test-of-Cure Visit was defined as 7 to 14 days after the completion of therapy rather than 48 hours posttreatment.

The clinical cure rate in this study was 83% for clarithromycin ER and 82% for clarithromycin IR. The bacteriological cure rate was 86% for clarithromycin ER and 85% for clarithromycin IR. In previous AECB studies, M90-418, M90-434, and M90-435,³ clarithromycin IR had a clinical cure rate of 51%, a clinical improvement rate of

44%, and a bacteriological cure rate of 90% [NDA 50-662 (S-004)]. The efficacy of both formulations is further supported by the similar clinical cure and bacteriological cure rates found in Studies M90-418, M90-434, and M90-435, even though efficacy endpoints were redefined.

Thus, the results of the previous studies may not be directly compared to the current study but can be used as a reference to support the continued strong efficacy of the clarithromycin IR formulation.

Clinical signs and symptoms of AECB resolved in subjects treated with either regimen, with no statistically significant differences between the treatment groups at Evaluation 2. At Evaluation 3, there were statistically significant differences between the groups in sputum appearance (purulent), with a higher resolution rate among subjects in the clarithromycin ER group (96%) than in the clarithromycin IR group (85%). Among clinically evaluable and intent-to-treat subjects at Evaluation 3, significant treatment differences were observed in coryza, with higher resolution rates in the clarithromycin IR (84% and 84%, respectively) group than in the clarithromycin ER group (70% and 71%, respectively).

Both clarithromycin formulations were safe and well tolerated. Excluding adverse events judged not related or probably not related to study drugs, the incidence of adverse events was similar in the treatment groups (22% clarithromycin ER; 17% clarithromycin IR). Most adverse events in both treatment groups were considered mild or moderate in intensity. Nine subjects in the each treatment group discontinued treatment due to adverse events. Adverse events leading to discontinuation were most frequently associated with the digestive system and body as a whole in the clarithromycin ER group, and with the digestive system in the clarithromycin IR group. Results of this study indicated that clarithromycin ER (2 x 500 mg QD for 7 days) was equivalent to clarithromycin IR (500 mg BID for 7 days) in treating adults with acute exacerbation of chronic bronchitis. Both treatment regimens were effective in eradicating the target pathogens and in resolving clinical signs and symptoms of AECB. Clarithromycin ER and clarithromycin IR were safe and well tolerated.

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INTEGRATED SUMMARY OF SAFETY:

All Treatment-Emergent Adverse Events in Studies M97-667 and M97-756

Studies M97-667 and M97-756 compared clarithromycin ER and clarithromycin IR. When adverse events in these two studies were analyzed, no statistically significant differences were observed between the two clarithromycin formulations in the overall incidence of adverse events or the incidence of adverse events grouped by body system. One or more adverse events were reported by 42% of the subjects in the clarithromycin ER group and by 37% of the subjects in the clarithromycin IR group. The most common adverse events in the clarithromycin ER and clarithromycin IR groups were associated with the digestive system (21% and 18%, respectively), body as a whole (11% and 11%, respectively), special senses (8% and 8%, respectively), and respiratory system (7% and 6%, respectively).

Overall, the most commonly reported (incidence $\geq 3\%$) adverse events in Studies M97-667 and M97-756 in the clarithromycin ER and clarithromycin IR groups were diarrhea (8% and 7%, respectively), taste perversion (6% and 6%, respectively), nausea (5% and 6%, respectively), and headache (5% and 5%, respectively). Statistically significant treatment differences were observed in the incidence of three adverse events. Abdominal pain was reported by 10 (2%) subjects in the clarithromycin ER group and one (0.2%) subject in the clarithromycin IR group ($p=0.011$); constipation was reported by six (1%) subjects in the clarithromycin ER group and no subject in the clarithromycin IR group ($p=0.031$). Conversely, dyspepsia was reported by two (0.4%) subjects in the clarithromycin ER group and 10 (2%) subjects in the clarithromycin IR group ($p=0.020$).

Most adverse events in both treatment groups were considered mild or moderate in intensity. Twenty (4%) subjects in the clarithromycin ER group reported 22 severe events. The most commonly reported severe events in the clarithromycin ER group included diarrhea and taste perversion by three subjects each and headache by two subjects; all other severe adverse events were reported by one subject each. Twenty-two (5%) subjects in the clarithromycin IR group reported 27 severe events. The most commonly reported severe events in the clarithromycin IR group included headache by six subjects; diarrhea by five subjects; and accidental injury, gastroenteritis, and nausea by two subjects each; all other severe adverse events were reported by one subject each.

A summary of all treatment-emergent adverse events reported by $\geq 1\%$ (five or more) of subjects in either treatment group is presented by treatment group in the table below; incidence of adverse events reported by four or fewer subjects is designated as $<1\%$.

Summary of Treatment-Emergent Adverse Event Incidence Rates ($\geq 1\%$) by COSTART Term (All Adverse Events in Studies M97-667 and M97-756)										
Adverse Events ^a	Clarithromycin ER (N=459) Severity ^b					Clarithromycin IR (N=444) Severity ^b				
	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Diarrhea	24	8	3	35	8%	16	8	5	29	7%
Taste perversion	18	6	3	27	6%	17	10	1	28	6%
Headache	11	11	2	24	5%	9	9	6	24	5%
Nausea	13	10	0	23	5%	14	10	2	26	6%
Oral moniliasis	5	5	0	10	2%	3	0	0	3	<1%
Abdominal pain*	4	6	0	10	2%	1	0	0	1	<1%
Gastritis	5	3	0	8	2%	0	3	1	4	<1%
Pharyngitis	4	4	0	8	2%	3	3	0	6	1%
Rhinitis	3	3	0	6	1%	6	3	0	9	2%
Constipation*	4	2	0	6	1%	0	0	0	0	0%
Lab test abnormal	4	0	0	5 ^c	1%	4	1	0	5	1%
Asthma	1	3	1	5	1%	0	2	0	2	<1%
Bronchitis	2	2	1	5	1%	0	1	0	1	<1%
Gastroenteritis	2	2	1	5	1%	0	2	2	4	<1%
Vertigo	4	1	0	5	1%	0	1	1	2	<1%
Vaginitis	2	2	0	4	<1%	2	3	0	5	1%
Otitis media	3	0	0	3	<1%	3	3	0	6	1%
Accidental injury	2	1	0	3	<1%	2	1	2	5	1%
Dyspepsia*	2	0	0	2	<1%	6	3	1	10	2%
Dry mouth	2	0	0	2	<1%	3	2	1	6	1%

Mod = moderate; Sev = severe
 * Indicates statistical significance at the 0.05 level.
 a Adverse events occurring in $\geq 1\%$ (five or more) of subjects in either treatment group.
 b Table summarizes the most severe occurrence of each COSTART term from each subject.
 c Severity of one adverse event was unknown.

Treatment-Emergent Adverse Events in Studies M97-667 and M97-756, Excluding Events Judged Not Related or Probably Not Related to Study Drugs

When adverse events excluding events judged not related or probably not related to study drugs in Studies M97-667 and M97-756 were analyzed, no statistically significant differences were observed between the two clarithromycin formulations in the overall incidence of adverse events or the incidence of adverse events grouped by body system. One or more adverse events judged possibly or probably related to study drug were reported by 25% of the subjects in the clarithromycin ER group and by 21% of the subjects in the clarithromycin IR group. The most common adverse events in the clarithromycin ER and clarithromycin IR groups excluding events judged not related or probably not related to study drugs were associated with the digestive (15% and 14%, respectively), special senses (6% and 6%, respectively), and body as a whole (3% and 3%, respectively) body systems.

Overall, the most commonly reported (incidence $\geq 3\%$) adverse events, excluding events judged not related or probably not related to study drugs, in Studies M97-667 and M97-756 in the clarithromycin ER and clarithromycin IR groups were taste perversion

(6% and 6%, respectively), diarrhea (6% and 5%, respectively), and nausea (3% and 5%, respectively). A statistically significant treatment difference was observed in the incidence of abdominal pain; abdominal pain was reported by seven (2%) subjects in the clarithromycin ER group and no subjects in the clarithromycin IR group (p=0.015).

A summary of all treatment-emergent adverse events reported by ≥1% (five or more) of subjects in either treatment group is presented by treatment group in the table below; incidence of adverse events reported by four or fewer subjects is designated as <1%.

Summary of Treatment-Emergent Adverse Event Incidence Rates (≥1%) by COSTART Term (Adverse Events in Studies M97-667 and M97-756 Excluding Events Judged Not Related or Probably Not Related to Study Drugs)										
Adverse Events ^a	Clarithromycin ER (N=459) Severity ^b					Clarithromycin IR (N=444) Severity ^b				
	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Diarrhea	20	6	1	27	6%	13	6	4	23	5%
Taste perversion	18	6	3	27	6%	17	9	1	27	6%
Nausea	10	5	0	15	3%	13	6	2	21	5%
Gastritis	5	2	0	7	2%	0	3	1	4	<1%
Oral moniliasis	4	3	0	7	2%	2	0	0	2	<1%
Abdominal pain*	4	3	0	7	2%	0	0	0	0	0%
Headache	2	5	0	7	2%	6	2	1	9	2%
Vaginitis	2	2	0	4	<1%	2	3	0	5	1%
Dyspepsia	2	0	0	2	<1%	5	3	0	8	2%
Dry mouth	1	0	0	1	<1%	3	1	1	5	1%

Mod = moderate; Sev = severe
 * Indicates statistical significance at the 0.05 level.
 a Adverse events occurring in ≥1% (five or more) of subjects in either treatment group.
 b Table summarizes the most severe occurrence of each COSTART term from each subject.

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MEDICAL OFFICER'S CONCLUSIONS

Study M97-667:

The Medical Officer concurs with the applicant's conclusions based upon the review of the clinical efficacy and safety data. In this study, the two tablet formulations were compared for clinical efficacy in the treatment of sinusitis and, as expected, there was no statistical difference in either clinical response or radiographic response. At the Test-of-Cure Visit (Visit 4), clinical cure rates were 85% in the clarithromycin ER group and 79% in the clarithromycin IR group. The radiographic success rates were 89% in the clarithromycin ER group and 91% in the clarithromycin IR group.

The efficacy of both clarithromycin formulations demonstrated by the clinical cure rates and radiographic success rates was supported by the low percentage of subjects who withdrew from the study due to insufficient improvement. Insufficient improvement was cited by only one evaluable subject (clarithromycin IR group) as the reason for discontinuing treatment; in addition, one clarithromycin ER subject and two clarithromycin IR subjects cited insufficient improvement as the reason for prematurely discontinuing from the study.

Both clarithromycin formulations were safe and well tolerated. Excluding adverse events judged not related to study drug, the incidence of adverse events was similar in the treatment groups (32% clarithromycin ER; 28% clarithromycin IR). Most adverse events in both treatment groups were considered mild or moderate in intensity. No serious adverse events were reported during the study. Six subjects in the clarithromycin ER group and 11 subjects in the clarithromycin IR group discontinued treatment due to adverse events, of which all but one were considered related to study drug. In the clarithromycin IR group, eight of 11 subjects discontinued due to at least one gastrointestinal adverse event.

Results of this study indicate that clarithromycin ER (500 mg x 2 QD for 14 days) is equivalent to clarithromycin IR (500 mg BID for 14 days) in the treatment of adult subjects with acute maxillary sinusitis. Both treatment regimens were effective in resolving the clinical signs and symptoms of sinusitis and in improving or resolving radiographic findings. Both clarithromycin ER and clarithromycin IR were safe and well tolerated.

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ON ORIGINAL**

Study M97-756:

In this study, the two formulations were compared for bacteriological and clinical efficacy in the treatment of AECB and, as expected, there were no statistically significant differences in bacteriological response, overall pathogen eradication, or clinical response. At the Test-of-Cure Visit (Evaluation 3) in clinically and bacteriologically evaluable subjects, bacteriological cure rates were 86% in the clarithromycin ER group and 85% in the clarithromycin IR group. Overall pathogen eradication rates were 86% in the clarithromycin ER group and 88% in the clarithromycin IR group. Clinical cure rates were also similar for subjects who took clarithromycin ER (83%) and clarithromycin IR (82%). The 95% CI demonstrated that the two treatments were equivalent in bacteriological response, overall pathogen eradication, and clinical response.

The efficacy of clarithromycin treatment in the eradication of five target pathogens was examined: *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *H. parainfluenzae*, and *S. aureus*. Three of the pathogens, *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*, were included for treatment by the current IR formulation; the remaining two pathogens, *S. aureus* and *H. parainfluenzae* were not. Based upon the data submitted, and reanalyzed by this Medical Officer, the total number of *H. parainfluenzae* isolated in the clarithromycin ER arm were 26, and out of 26 isolates, 20 were pure cultures. The eradication rate was 19/20 (95%). In the clarithromycin IR arm, the numbers of isolates were 28, and out of those 28 isolates, 19 were pure cultures. The eradication rate in the IR arm was 17/19 (89%).

The total number of *S. aureus* isolated in the clarithromycin ER arm were 12, and out of 12 isolates, 8 were pure cultures. The eradication rate was 6/8 (75%). In the clarithromycin IR arm, the number of isolates were 11, and out of those 11 isolates, 6 were pure cultures. The eradication rate in the IR arm was 5/6 (83%).

Thus, based upon the above results, it is recommended that *H. parainfluenzae* be added to the list of organisms to both the IR Biaxin and the ER Biaxin labeling under the indication AECB. The addition of *S. aureus* to the AECB indication is not recommended at this time since the eradication rate of 75% is not acceptable, and the number of pure isolates of *S. aureus* was small.

Clinical signs and symptoms of AECB resolved in subjects treated with either regimen, with no statistically significant differences between the treatment groups at Evaluation 2. At Evaluation 3, there were statistically significant differences between the groups in sputum appearance (purulent), with a higher resolution rate among subjects in the clarithromycin ER group (96%) than in the clarithromycin IR group (85%). Among clinically evaluable and intent-to-treat subjects at Evaluation 3, significant treatment differences were observed in coryza, with higher resolution rates in the clarithromycin IR (84% and 84%, respectively) group than in the clarithromycin ER group (70% and 71%, respectively).

Both clarithromycin formulations were safe and well tolerated. Excluding adverse events judged not related or probably not related to study drugs, the incidence of adverse events was similar in the treatment groups (22% clarithromycin ER; 17% clarithromycin IR).

Most adverse events in both treatment groups were considered mild or moderate in intensity. Nine subjects in the each treatment group discontinued treatment due to adverse events. Adverse events leading to discontinuation were most frequently associated with the digestive system and body as a whole in the clarithromycin ER group, and with the digestive system in the clarithromycin IR group.

Results of this study indicated that clarithromycin ER (2 x 500 mg QD for 7 days) was equivalent to clarithromycin IR (500 mg BID for 7 days) in treating adults with acute exacerbation of chronic bronchitis. Clarithromycin ER and clarithromycin IR were safe and well tolerated.

MEDICAL OFFICER'S RECOMMENDATIONS

It is recommended that NDA 50-775 for Biaxin XL Filmtab be approved for the indications of acute sinusitis and AECB due to microorganisms as described in the Division's proposed package insert. The draft package insert is reviewed under separate cover.

/S/

Nasim Moledina, M.D.
Medical officer, DAIDP.

CC: Original NDA 50-775

HFD-340

HFD-520

HFD-520/DepDir/LGavrilovich

HFD-520/MO/NMoledina 2/2/2000

HFD-520/Pharm/ROsterberg

HFD-520/Micro/ASheldon

HFD-520/Chem/SPagay

HFD-725/Biostat/JJiang

HFD-420/BioPharm/HSun

HFD-520/PM/JCintron

nm/02-08-2000.

Concurrence Only:

HFD-520/DivDir/GChikami

HFD-520/MTL/MSAlbuerne **/S/** 2/8/00

/S/ 2/2/2000