

differences were observed in clinical cure rates overall or after adjusting for potentially influential factors . The drop in cure rate in the intent-to-treat population compared to the clinically evaluable population is mainly due to the fact that subjects with indeterminate clinical response were treated as failures in the intent-to-treat analyses.

**Additional Investigator Assessment of Clinical Response**

No statistically significant differences were observed between the treatment groups in clinical cure rates for the additional investigator assessment at the Test-of-Cure Visit. Among clinically evaluable subjects, 85% of the clarithromycin ER group and 79% of the clarithromycin IR group were considered to be cured according to the revised definition. The 95% CI for the difference between clinical cure rates (clarithromycin ER - clarithromycin IR) based on the additional investigator assessment demonstrated that the two treatments were equivalent. A summary of the clinical cure rates for the clinically evaluable population is presented in the table below:

<b>Clinical Cure Rates at the Test-of-Cure Visit Based on the Additional Investigator Assessment (Clinically Evaluable Population)</b>			
	<u>Clarithromycin ER</u>	<u>Clarithromycin IR</u>	
	n/N (%)	n/N (%)	P-value <sup>b</sup>
	[95% CI] <sup>a</sup>	[95% CI] <sup>a</sup>	[95% CI] <sup>c</sup>
Clinical Cure Rate	104/122 (85%) [77.7, 91.0]	97/123 (79%) [70.6, 85.7]	0.244 [-3.2, 16.0]
A Exact binomial confidence interval.			
B P-value is from a Fisher's exact test comparing treatment groups.			
C Binomial confidence interval based on normal approximation.			

Clinical cure rates based on the additional investigator assessment were also compared between treatment groups using Cochran-Mantel-Haenszel methodology adjusting for country, investigator, sex, race, age, weight, overall clinical condition, infection status, number of sinus infections in the past 12 months, nasal polyps, deviated septum, allergic rhinitis, other nasal abnormality, any of the nasal abnormalities, study drug duration, and study drug compliance. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Fourteen subjects, five in the clarithromycin ER group and nine in the clarithromycin IR group, had their responses assigned at Visit 5. Based on the additional investigator assessments, four subjects in the clarithromycin ER group were assigned a response of cure and one was assigned a response of failure; five subjects in the clarithromycin IR group were assigned a response of cure and four were assigned a response of failure.

Results of the additional investigator assessment in the intent-to-treat population also demonstrated that the two treatments were equivalent. Clinical cure rates at the Test-of-

Cure Visit were 78% in the clarithromycin ER group and 73% in the clarithromycin IR group. No significant differences were observed in clinical cure rates overall or after adjusting for potentially influential factors.

### Secondary Efficacy Variables

#### Radiographic Resolution Rate

No statistically significant differences were observed between the treatment groups in radiographic resolution rates at the Test-of-Cure Visit. Among clinically evaluable subjects, 61% of the clarithromycin ER group and 64% of the clarithromycin IR group demonstrated radiographic resolution of sinusitis. The 95% CI for the difference between radiographic resolution rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. A summary of the radiographic resolution rate at the Test-of-Cure Visit is presented in the table below for the clinically evaluable subject population.

Radiographic Resolution Rates at the Test-of-Cure Visit (Clinically Evaluable Population)					
	Clarithromycin ER		Clarithromycin IR		P-value <sup>b</sup>
	n/N (%)		n/N (%)		[95% CI] <sup>c</sup>
	[95% CI] <sup>a</sup>		[95% CI] <sup>a</sup>		
Radiographic Resolution Rate <sup>d</sup>	68/111 (61%)		68/107 (64%)		0.780
	[51.5, 70.4]		[53.7, 72.6]		[-15.1, 10.6]
a Exact binomial confidence interval.					
b P-value is from a Fisher's exact test comparing treatment groups.					
c Binomial confidence interval based on normal approximation.					
d Missing responses were excluded from the calculation of radiographic response rates.					

#### Radiographic Success Rate

No statistically significant differences were observed between treatment groups in radiographic success rates at the Test-of-Cure Visit. Among clinically evaluable subjects, 89% of the clarithromycin ER group and 91% of the clarithromycin IR group demonstrated radiographic resolution or improvement in sinusitis. Five (4%) subjects in the clarithromycin ER group and two (2%) subjects in the clarithromycin IR group had radiographic evidence of worsening. The 95% CI for the difference between radiographic success rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. A summary of the radiographic success rate at the Test-of-Cure Visit is presented in the table below for the clinically evaluable subject population.

<b>Radiographic Success Rate at the Test-of-Cure Visit (Clinically Evaluable Population)</b>			
	<u>Clarithromycin ER</u>	<u>Clarithromycin IR</u>	<u>P-value<sup>c</sup></u>
	n/N (%) [95% CI] <sup>b</sup>	n/N (%) [95% CI] <sup>b</sup>	[95% CI] <sup>d</sup>
Radiographic Success Rate <sup>d</sup>	99/111 (89%) [81.9, 94.3]	97/107 (91%) [83.5, 95.4]	0.823 [-9.5, 6.5]
<p>a Exact binomial confidence interval.</p> <p>b P-value is from a Fisher's exact test comparing treatment groups.</p> <p>c Binomial confidence interval based on normal approximation.</p> <p>d Missing responses were excluded from calculation of radiographic response rates.</p>			

Radiographic resolution rates and radiographic success rates were also compared between treatment groups using Cochran-Mantel-Haenszel methodology adjusting for country, investigator, sex, race, age, weight, overall clinical condition, infection status, number of sinus infections in the past 12 months, nasal polyps, deviated septum, allergic rhinitis, other nasal abnormality, any of the nasal abnormalities, study drug duration, and study drug compliance. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups in radiographic resolution rates or radiographic success rates.

Results of the radiographic resolution rates and radiographic success rates in the intent-to-treat population also demonstrated that the two treatments were equivalent. Radiographic resolution rates at the Test-of-Cure Visit were 53% in both treatment groups; radiographic success rates were 76% in the clarithromycin ER group and 75% in the clarithromycin IR group. No significant differences were observed in radiographic resolution rates and radiographic success rates overall or after adjusting for potentially influential factors.

### Clinical Signs and Symptoms

At Visit 3, there were no statistically significant differences between treatment groups in the percentage of subjects showing resolution or resolution/improvement in sinus headache, sinus pain, or sinus tenderness, or resolution in facial erythema, nasal congestion, facial swelling, purulent nasal discharge, or fever in the clinically evaluable subject population. A summary of the resolution and resolution/improvement rates for all signs and symptoms at Visit 3 is presented in the table below for the clinically evaluable subject population.

<b>Resolution and/or Improvement of Pretreatment<sup>a</sup> Signs/Symptoms Compared to Visit 3 (Clinically Evaluable Population)</b>					
<u>Sign/Symptom</u>	<u>Clarithromycin</u> <u>ER</u>		<u>Clarithromycin</u> <u>IR</u>		<u>P-value<sup>b</sup></u>
<u>Sinus Headache</u>					
Resolution	80 /96	(83%)	78 /97	(80%)	0.709
Resolution/Improvement	89 /96	(93%)	87 /97	(90%)	0.613
<u>Sinus Pain</u>					
Resolution	86 /99	(87%)	82 /101	(81%)	0.336
Resolution/Improvement	92 /99	(93%)	94 /101	(93%)	>0.999
<u>Sinus Tenderness</u>					
Resolution	85 /100	(85%)	77 /97	(79%)	0.353
Resolution/Improvement	96 /100	(96%)	87 /97	(90%)	0.101
<u>Facial Erythema</u>					
Resolution	21 /24	(88%)	28 /32	(88%)	>0.999
<u>Nasal Congestion</u>					
Resolution	69 /113	(61%)	67 /110	(61%)	>0.999
<u>Facial Swelling</u>					
Resolution	38 /43	(88%)	34 /42	(81%)	0.382
<u>Purulent Nasal Discharge</u>					
Resolution	85 /98	(87%)	97 /107	(91%)	0.387
<u>Fever</u>					
Resolution	23 /24	(96%)	27 /28	(96%)	>0.999

a Pretreatment assessment was made before or on Study Day 1; Visit 3 assessment was made 0 to 5 days posttreatment.

b P-values are from a 2 x 2 Fisher's exact test comparing treatment groups.

In the intent-to-treat population, a statistically significant difference was observed in sinus tenderness at Visit 3, with a higher percentage of subjects in the clarithromycin ER group (96%) than in the clarithromycin IR group (88%) showing resolution or improvement in sinus tenderness (p=0.036).

At the Test-of-Cure Visit (Visit 4), there were no statistically significant differences between treatment groups in the percentage of subjects showing resolution or resolution/improvement in sinus headache, sinus pain, or sinus tenderness, or resolution in facial erythema, nasal congestion, facial swelling, purulent nasal discharge, or fever in the clinically evaluable subject population. A summary of the resolution and resolution/improvement rates for all signs and symptoms at Visit 4 is presented in the table below for the clinically evaluable subject population.

Resolution and/or Improvement of Pretreatment <sup>a</sup> Signs/Symptoms Compared to Visit 4 (Clinically Evaluable Population)					
<u>Sign/Symptom</u>	<u>Clarithromycin ER</u>		<u>Clarithromycin IR</u>		<u>P-value<sup>b</sup></u>
<u>Sinus Headache</u>					
Resolution	74 /94	(79%)	75 /94	(80%)	>0.999
Resolution/Improvement	86 /94	(91%)	84 /94	(89%)	0.805
<u>Sinus Pain</u>					
Resolution	84 /98	(86%)	84 /97	(87%)	>0.999
Resolution/Improvement	93 /98	(95%)	93 /97	(96%)	>0.999
<u>Sinus Tenderness</u>					
Resolution	88 /98	(90%)	81 /93	(87%)	0.652
Resolution/Improvement	95 /98	(97%)	87 /93	(94%)	0.321
<u>Facial Erythema</u>					
Resolution	22 /23	(96%)	28 /28	(100%)	0.451
			)		
<u>Nasal Congestion</u>					
Resolution	74 /111	(67%)	70 /105	(67%)	>0.999
<u>Facial Swelling</u>					
Resolution	39 /42	(93%)	35 /39	(90%)	0.706
<u>Purulent Nasal Discharge</u>					
Resolution	86 /98	(88%)	89 /102	(87%)	>0.999
<u>Fever</u>					
Resolution	23 /26	(88%)	28 /29	(97%)	0.335

a Pretreatment assessment was made before or on Study Day 1. Visit 4 (test-of-cure) assessment was made at least 7 days posttreatment.

b P-values are from a 2 x 2 Fisher's exact test comparing treatment groups.

**Applicant's Efficacy Conclusions**

Clinical cure rates based on the additional investigator assessment at the Test-of-Cure Visit were similar for clinically evaluable subjects who received clarithromycin ER (85%) and clarithromycin IR (79%), with no statistically significant treatment differences. The 95% CI demonstrated that the two treatments were equivalent in clinical response. Similarly, radiographic resolution rates and radiographic success rates at the Test-of-Cure Visit were similar for clinically evaluable subjects who received clarithromycin ER (61% and 89%, respectively) and clarithromycin IR (64% and 91%, respectively), with no statistically significant differences. The 95% CI demonstrated that the two treatments were equivalent in radiographic response.

Clinical signs and symptoms of sinusitis resolved in subjects treated with either regimen, with no statistically significant differences between the treatment groups among clinically

evaluable subjects at Visit 3 or Visit 4. Results of this study indicate that clarithromycin ER (500 mg x 2 QD for 14 days) was equivalent to clarithromycin IR (500 mg BID for 14 days) in treating acute maxillary sinusitis in adult subjects. Similar results were observed in the intent-to-treat population.

### Safety Evaluations

All subjects who received at least one dose of study drug (N=283) were included in the safety analyses (all treated subjects population).

### Extent of Exposure

Of the 142 subjects assigned to clarithromycin ER, 94% of the subjects completed at least 11 days of the 14-day treatment regimen. Of the 141 subjects assigned to clarithromycin IR, 88% of the subjects completed at least 11 days of the 14-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	142	141
<u>Duration of Treatment (Days)</u>		
<3	0 ( 0%)	2 ( 1%)
3 - <11	9 ( 6%)	15 (11%)
≥11	133 (94%)	124 (88%)
Mean (SD)	13.8 (2.37)	13.3 (3.20)
Min - Max	3 - 19	1 - 16

### ADVERSE EVENTS

#### Brief Summary of Adverse Events

The incidences of all treatment-emergent adverse events including or excluding events judged not related to study drug were 50% and 32%, respectively, in the clarithromycin ER group and 50% and 28%, respectively, in the clarithromycin IR group. The most frequently occurring adverse events excluding those judged not related to study drug in both treatment groups were taste perversion, diarrhea, and nausea.

No subjects in either treatment group had a serious adverse event during the study. Seventeen subjects (six clarithromycin ER and 11 clarithromycin IR) were prematurely discontinued from treatment due to the occurrence of at least one adverse event. In the clarithromycin IR group, eight of 11 subjects discontinued treatment due to at least one gastrointestinal adverse event.

Of the 283 randomized subjects who received study drug, 71 subjects (50%) in each treatment group reported at least one adverse event during the study. Overall, the most commonly reported adverse events in the clarithromycin ER and clarithromycin IR groups included taste perversion (10% and 11%, respectively), headache (9% and 10%, respectively), nausea (9% and 11%, respectively), and diarrhea (8% and 9%, respectively). A statistically significant difference was observed between treatment groups in the incidence of abdominal pain ( $p=0.030$ ); six (4%) subjects in the clarithromycin ER group and no subject in the clarithromycin IR group reported abdominal pain. Most adverse events in both treatment groups were considered mild or moderate in intensity. Two subjects in the clarithromycin ER group reported two severe events (one report each of headache and rash) and eight subjects in the clarithromycin IR group reported 11 severe events (three reports of headache, and one report each of accidental injury, asthenia, back pain, diarrhea, gastroenteritis, nausea, vertigo, and taste perversion).

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 <sup>a</sup>	Clarithromycin ER (N=142)					Clarithromycin IR (N=141)				
	Severity <sup>b</sup>			Total	%	Severity <sup>b</sup>			Total	%
Mild	Mod	Sev	Mild			Mod	Sev			
OVERALL <sup>c</sup>	34	35	2	71	50%	32	31	8	71	50%
Taste Perversion	10	4	0	14	10%	8	6	1	15	11%
Headache	7	5	1	13	9%	4	7	3	14	10%
Nausea	7	5	0	12	9%	10	4	1	15	11%
Diarrhea	8	3	0	11	8%	8	4	1	13	9%
Abdominal Pain <sup>*</sup>	4	2	0	6	4%	0	0	0	0	0%
Rhinitis	2	3	0	5	4%	5	3	0	8	6%
Dyspepsia	2	0	0	2	1%	5	0	0	5	4%

Mod = moderate; Sev = severe  
<sup>\*</sup> Indicates statistical significance at the 0.05 level.  
<sup>A</sup> Adverse events occurring in  $\geq 3\%$  of subjects in either treatment group.  
<sup>B</sup> Table summarizes the most severe occurrence of each COSTART term from each subject.  
<sup>C</sup> Number of subjects with one or more adverse events.

When events judged not related to study drugs were excluded, 32% (45/142) of subjects in the clarithromycin ER group and 28% (40/141) 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 adverse events excluding those judged not related to study drug were taste perversion (14/142, 10%), diarrhea (8/142, 6%), and nausea (7/142, 5%) in the clarithromycin ER group and taste perversion (14/141, 10%), nausea (12/141, 9%), and diarrhea (11/141, 8%) in the clarithromycin IR group. Severe drug-related adverse events were reported by one subject in the clarithromycin ER group (rash) and four subjects in the clarithromycin IR group (one report each of diarrhea, gastroenteritis, nausea, and taste perversion). A summary of treatment-emergent adverse

events, excluding events judged not related or probably not related to study drugs, reported by  $\geq 1\%$  of subjects in either treatment group is presented by treatment group in the table below:

Summary of Treatment-Emergent Adverse Event Incidence Rates by COSTART Term (Excluding Events Judged Not Related or Probably Not Related to Study Drugs)										
Adverse Events <sup>a</sup>	Clarithromycin ER (N=142) Severity <sup>b</sup>					Clarithromycin IR (N=141) Severity <sup>b</sup>				
	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL <sup>c</sup>	30	14	1	45	32%	24	12	4	40	28%
Taste Perversion	10	4	0	14	10%	8	5	1	14	10%
Diarrhea	7	1	0	8	6%	7	3	1	11	8%
Nausea	6	1	0	7	5%	9	2	1	12	9%
Abdominal Pain	4	1	0	5	4%	0	0	0	0	0%
Vaginal Moniliasis	2	1	0	3	2%	1	0	0	1	<1%
Dyspepsia	2	0	0	2	1%	4	0	0	4	3%
Gastritis	2	0	0	2	1%	0	2	0	2	1%
Myalgia	2	0	0	2	1%	0	0	0	0	0%
Vaginitis	1	1	0	2	1%	1	2	0	3	2%
Headache	1	1	0	2	1%	2	1	0	3	2%
Dry Mouth	1	0	0	1	<1%	2	0	0	2	1%
Lab Test Abnormal	0	0	0	0	0%	2	0	0	2	1%
Vomiting	0	0	0	0	0%	1	1	0	2	1%

Mod = moderate; Sev = severe

a Adverse events occurring in  $\geq 1\%$  of subjects in either treatment group.  
 B Table summarizes most severe occurrence of each COSTART term from each subject.  
 C Number of subjects with one or more adverse events.

### Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths or serious adverse events were reported during the study.

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

#### Significant Adverse Events

No subject treated with clarithromycin ER or clarithromycin IR experienced a serious adverse event during the study.

Six subjects in the clarithromycin ER group and 11 subjects in the clarithromycin IR group were prematurely discontinued from treatment due to the occurrence of at least one adverse event. All but one adverse event leading to discontinuation of study drug was considered to be possibly or probably related to study drug. In the clarithromycin IR group, eight of 11 subjects discontinued treatment due to at least one gastrointestinal adverse event. Details concerning subjects who discontinued treatment due to adverse events are displayed by treatment group in the table below:

Subjects Who Prematurely Discontinued Treatment Due to Adverse Events					
Investigator, Subject Number	Age (yrs)/ Sex	Day of Onset	Day of Resolution <sup>a</sup>	Body System	COSTART Term
<b>Subjects Discontinued from the Clarithromycin ER Treatment Group</b>					
Dixon 6304	28/F	4	5 (1)	Cardiovascular	Palpitation <sup>b</sup>
		4	5 (1)	Digestive	Dyspepsia <sup>b</sup>
		4	5 (1)	Skin & Appendages	Sweating <sup>b</sup>
		4	5 (1)	Special Senses	Taste perversion <sup>b</sup>
McCluskey 6284	41/M	8	15 (6)	Digestive	Gastrointestinal moniliasis <sup>b</sup>
Smith 6220	63/M	4	16 (10)	Musculoskeletal	Myalgia <sup>b</sup>
Smith 6314	33/F	9	Ongoing	Metabolic & Nutritional Disorders	Peripheral edema <sup>b</sup>
		9	Ongoing	Nervous	Paresthesia <sup>b</sup>
Solomon 6232	48/M	7 (1)	13 (7)	Body as a Whole	Headache
Solomon 6352	76/M	4	8 (2)	Skin & Appendages	Rash <sup>b</sup>
<b>Subjects Discontinued from the Clarithromycin IR Treatment Group</b>					
Dixon 6303	69/F	5	10 (3)	Digestive	Dyspepsia <sup>b</sup>
		5	10 (3)	Digestive	Nausea <sup>b</sup>
		5	10 (3)	Special Senses	Taste perversion <sup>b</sup>
Dixon 6543	37/F	4	6 (2)	Digestive	Nausea <sup>b</sup>
		4	6 (2)	Digestive	Vomiting <sup>b</sup>
Dixon 6546	25/M	1	4 (1)	Digestive	Nausea <sup>b</sup>
Imam 6254	43/M	3	3	Body as a Whole	Headache <sup>b</sup>
Lentnek 6176	20/F	1	1	Digestive	Nausea <sup>b</sup>
		5	9 (4)	Urogenital	Vaginitis <sup>b</sup>
Matz 6265	33/M	2	4 (1)	Digestive	Diarrhea <sup>b</sup>
		2	4 (1)	Digestive	Gastritis <sup>b</sup>
		2	4 (1)	Digestive	Vomiting <sup>b</sup>
McCluskey 6147	24/F	8	13 (1)	Special Senses	Taste perversion <sup>b</sup>
McNellis 6238	37/M	2	Ongoing	Digestive	Diarrhea <sup>b</sup>
Solomon 6235	35/F	1	2 (1)	Digestive	Nausea <sup>b</sup>
Solomon 6351	17/M	2	4 (2)	Digestive	Diarrhea <sup>b</sup>
		2	4 (2)	Digestive	Nausea <sup>b</sup>
Wald 6590	30/F	1	11 (1)	Special Senses	Taste perversion <sup>b</sup>
a Numbers in parentheses are days relative to last dose of study drug.					
b Drug-relationship classified as possible or probable.					

## Clinical Laboratory Evaluation

### Evaluation of Each Laboratory Parameter

#### Laboratory Values Over Time

Minor increases and decreases from baseline in mean values for laboratory variables were observed in both treatment groups, none of which were considered to be clinically meaningful.

### **Individual Clinically Significant Abnormalities**

No subject in either treatment group had a hematology or serum chemistry value which met the sponsor-defined criteria for possibly clinically significant.

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

Minor increases and decreases from baseline 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.

Two subjects had values for vital signs that met sponsor-defined possibly clinically significant criteria. Murray Subject 6317 had an increase in diastolic blood pressure (baseline value: 74 mmHg) of more than 30 mmHg to a value above 105 mmHg (106 mmHg) on Study Day 15, 7 days after the last dose of study drug. Schworer Subject 6357 had a decrease in body temperature more than two degrees from baseline; as this subject had a fever at baseline (100.9°F), the decrease brought his temperature to within normal range: 97.8°F on Study Day 15, 1 day after the last dose of study drug, and 98.8°F on Study Day 27, 13 days after the last dose of study drug. Neither of these changes in vital signs was considered by the investigator to be of clinical concern.

### **Applicant's Safety Conclusions**

The incidences of all treatment-emergent adverse events and adverse events excluding those judged unrelated to study drug were similar between the treatment groups. The most frequently occurring adverse events in both treatment groups, excluding those events judged not related to study drug, were taste perversion, diarrhea, and nausea.

No serious adverse events were reported during the study. Seventeen subjects (six clarithromycin ER and 11 clarithromycin IR) were prematurely discontinued from treatment due to the occurrence of at least one adverse event; all but one (probably not related to study drug) of these subjects had adverse events that were considered to be related to study drug.

Changes in laboratory and vital signs variables were minor and not considered clinically meaningful.

### **Applicant's Overall Conclusions**

Clarithromycin immediate release tablets and clarithromycin granules for oral suspension are indicated for the treatment of acute maxillary sinusitis 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 Area Under the Curve over 24 hours, 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 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, based on the additional investigator assessment. 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 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.

The primary endpoint for efficacy was 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 10 to 17 days posttreatment rather than 48 hours posttreatment.

The clinical cure rate in this study was 85% for clarithromycin ER and 79% for clarithromycin IR. In study M90-417 [NDA 50-662 (S-004)] the clarithromycin IR clinical cure rate at 48 hours post-treatment was 64% and clinical improvement rate was 33%. Radiographic success rates for clarithromycin IR in both studies were similar (91% in the current study and 88% in study M90-417). The efficacy of both formulations is further supported by the similar clinical cure and radiographic success rates found in study M90-417 even though efficacy endpoints were redefined.

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.

**Review of Study M97-756:**

**A Comparative Study of the Efficacy and Safety of Clarithromycin Extended Release Tablets and Clarithromycin Immediate Release Tablets for the Treatment of Subjects with Acute Exacerbation of Chronic Bronchitis**

Study Identification: M97-756

Study Phase: 3

Name of Drug: Clarithromycin Extended Release (Abbott-56268)

Indication: Acute Exacerbation of Chronic Bronchitis

Structure: Randomized

Blinding: Double-Blind

Duration of Therapy: 7 days, clarithromycin extended release (ER); 7 days, clarithromycin immediate release (IR)

Investigators: 113 investigators (multicenter); 87 investigators enrolled subjects in the United States (US) and Canada

Method of Subject

Assignment: Subjects were randomly assigned in a 1:1 ratio at each investigational site to receive either clarithromycin extended release tablets, 1 gram (2 - 500 mg tab) once a day (QD) for 7 days, or clarithromycin immediate release tablets, 1 gram, 500 mg twice a day (BID) for 7 days.

Study Initiation: March 10, 1998

Study Completion: February 22, 1999

Synopsis

<b>Name of Company:</b> Abbott Laboratories		
<b>Name of Finished Product:</b> Clarithromycin ER (A-56268)		
<b>Name of the Active Ingredient:</b> 6-0-methylerythromycin A		
<b>Title of Study:</b> A Comparative Study of the Efficacy and Safety of Clarithromycin Extended Release Tablets and Clarithromycin Immediate Release Tablets for the Treatment of Subjects with Acute Exacerbation of Chronic Bronchitis		
<b>Investigator(s):</b> 87 investigator sites enrolled subjects	<b>Study Center:</b> [redacted] United States and Canada	
<b>Publication (reference):</b> N/A		
<b>Study Period (years):</b> Date of First Enrollment: March 10, 1998 Date of Last Completed: February 22, 1999	<b>Phase of Development:</b> 3	
<b>Objectives:</b> The primary objective of this study was to compare the efficacy and safety of a 7-day course of therapy with clarithromycin extended release tablets (2 x 500 mg QD) with those of a 7-day course of therapy with clarithromycin immediate release tablets (1 x 500 mg BID) in the treatment of ambulatory subjects with acute exacerbation of chronic bronchitis (AECB).		
<b>Methodology:</b> This was a Phase 3, double-blind, randomized, parallel-group, multicenter study in ambulatory subjects with acute exacerbation of chronic bronchitis (AECB). Subjects were randomly assigned in a 1:1 ratio at each investigational site to receive either: clarithromycin extended release (ER) tablets, 2 x 500 mg QD for 7 days, or clarithromycin immediate release (IR) tablets, 500 mg BID for 7 days. Approximately 300 subjects were planned to be enrolled per treatment group. Subjects returned for Evaluation 2 within 48 hours posttreatment. Subjects returned once during Study Days 19-21 (Evaluation 3) for a Test-of-Cure Visit. Safety was evaluated throughout the subject's study participation by periodic laboratory tests, posttreatment physical examination, and monitoring of adverse events.		
<b>Number of Subjects (planned and analyzed)</b>	<b>Clarithromycin ER</b>	<b>Clarithromycin IR</b>
Number of Subjects Planned	300	300
Number of Subjects Randomized	320	307
Number of Subjects Treated	317	303
Intent-to-Treat Analyses	300	285
Excluded from Intent-to-Treat Analyses	17	18
Clinically Evaluable Analyses	261	259
Excluded from Clinically Evaluable Analyses	56	44
Clinically & Bacteriologically Evaluable Analyses	100	82
Excluded from Clinically & Bacteriol. Evaluable Analyses	217	221
No target pathogen isolated pretreatment	181	193
Selection criteria not met	22	18
Disqualified investigator (12312, Feicht)	7	6
Did not return for Test-of-Cure Visit	3	3
Used confounding medication and noncompliance	4	1
Subjects Included in the Safety Analyses	317	303

<b>Name of Company:</b> Abbott Laboratories			
<b>Name of Finished Product:</b> Clarithromycin ER (A-56268)			
<b>Name of the Active Ingredient:</b> 6-O-methylerythromycin A			
<b>Diagnosis and Main Criteria for Inclusion:</b> Males and females 12 years of age or older were enrolled if they had a medical history of chronic bronchitis, a productive cough with an acceptable purulent sputum sample, and a presumptive diagnosis of AECB with onset of signs and symptoms (cough, fever, hoarseness, wheezing) within 14 days prior to Evaluation 1 that was suitable for oral antibiotic therapy.			
<b>Test Product, Dose and Mode of Administration, Batch Number:</b>			
<u>Test Product</u>	<u>Dose</u>	<u>Mode of Administration</u>	<u>Finishing Lot Batch Number</u>
			USA                      Canada
Clarithromycin extended release tablets	2 x 500 mg QD for 7 days	Oral	33-249-S2              40-318-S2 40-296-S2
<b>Reference Therapy, Dose and Mode of Administration, Batch Number:</b>			
<u>Test Product</u>	<u>Dose</u>	<u>Mode of Administration</u>	<u>Finishing Lot Batch Number</u>
			USA                      Canada
Clarithromycin immediate release tablets	500 mg BID for 7 days	Oral	36-641-S2              40-320-S2 40-298-S2
<b>Duration of Treatment:</b> 7 days of treatment			
<b>Criteria for Evaluation (Evaluated before unblinding):</b>			
<b>Clinically Evaluable Analysis:</b> All of the following criteria were to be satisfied for a subject to be considered eligible for clinical efficacy analysis:			
<ul style="list-style-type: none"> <li>• The subject had taken study drug for a minimum of 3 full days to qualify for efficacy evaluation as a clinical failure; to qualify as a clinical cure, the subject had taken at least 80% of prescribed study medication.</li> <li>• The subject did not receive any other antimicrobial agent during the period 21 days prior to the start of study drug through the subject's final clinical visit unless the subject was considered a study treatment failure or the antimicrobial agent was not considered to have had an effect on the infection.</li> <li>• 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.</li> <li>• The subject did not violate any selection criteria unless it was considered not to affect the efficacy evaluation.</li> <li>• An efficacy evaluation was conducted 7-23 days posttreatment (Test-of-Cure Visit) unless the subject was a treatment failure prior to this time.</li> </ul>			
<b>Clinically and Bacteriologically Evaluable Analysis:</b> In addition to the above conditions, subjects must have had at least one target pathogen ( <i>H. influenzae</i> , <i>S. pneumoniae</i> , <i>M. catarrhalis</i> , <i>H. parainfluenzae</i> , or <i>S. aureus</i> ) isolated at pretreatment based on an acceptable gram stain ( $\leq 10$ squamous epithelial cells and $\geq 25$ polymorphonucleated leukocytes per low power field).			
<b>Intent-to-Treat Analysis:</b> 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 analyses.			
<b>All Treated Subjects Safety Analysis:</b> All subjects who received at least one dose of study medication were included in the all treated subjects safety analysis.			

<b>Name of Company:</b> Abbott Laboratories		
<b>Name of Finished Product:</b> Clarithromycin Extended Release (ER) (A-56268)		
<b>Name of the Active Ingredient:</b> 6-0-methylerythromycin A		
<b>Statistical Methods:</b> Statistical tests were based on two-tailed tests with the 0.05 significance level and 95% confidence interval (CI). Exact binomial 95% CI was constructed for each of the two treatment groups for each efficacy variable. Binomial 95% CI were computed for the difference between treatment groups (extended release – immediate release) in efficacy variables. Clinical cure rates, subject bacteriological cure rates, and pathogen eradication rates were the primary efficacy variables. Change in clinical signs and symptoms was the secondary efficacy variable.		

### Investigative Sites

One hundred thirteen (113) investigators in the US and Canada were recruited to perform the study and received study drug supplies; 87 of these investigators (79 in the US and eight in Canada) enrolled subjects into the study. A total of 627 subjects were enrolled; six subjects did not return after Evaluation 1 and one subject was discontinued before taking study drug due to a selection criteria violation (allergy to macrolide antibiotics). There was no evidence that these seven subjects took any study drug; hence, they were excluded from all analyses. These seven subjects were 4154, 4156, 4157, and 4159 from Dewan (Investigator No. 9624), 3987 and 4234 from Dotson (Investigator No. 13533), and 3309 from Fox (Investigator No. 13647). The study was conducted from March 10, 1998 to February 22, 1999. The distribution of all treated subjects for each investigator is presented in the table below:

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Distribution of All Treated Subjects by Investigator					
Investigator	Clarithromycin ER	Clarithromycin IR	Investigator	Clarithromycin ER	Clarithromycin IR
Adler	3	2	Mansfield	4	3
Allen	13	13	McCarty <sup>a</sup>	1	2
Angelo	4	3	Milgrom	4	4
Arno	2	1	Miller	7	6
Bell	1	0	Moriarty	8	8
Bensch	7	8	Morowitz	6	4
Bernstein	2	2	Munk	6	5
Bowman	1	1	Nayak	6	5
Brazinsky	8	8	Ondrejicka	2	2
Bruya	7	7	Onuska <sup>a</sup>	3	2
Caldwell	1	2	Peshimam	3	3
Chiambretti	2	2	Phillips	0	1
Chien <sup>a</sup>	0	1	Razzetti	1	1
Cox	2	2	Resnick	2	2
Culver	1	0	Rictor	0	1
Cutler	3	4	Rollins	7	7
Dattani <sup>a</sup>	5	5	Rosenthal	2	0
David	3	3	Sack	2	1
Dengiz	1	0	Safdi	2	3
Desai	2	2	Saff	6	4
Dewan	20	20	Sant Ram	0	1
Dotson	9	7	Schenkel	4	2
Feicht	7	6	Schmitz	0	1
Feldstein	1	1	Schneider	10	10
Fisher	2	2	Schul	4	4
Gellrick	4	4	Scott	1	1
Given	2	0	Shah	2	3
Gohill	1	1	Siarni	20	20
Guzzetta	3	4	Singh	6	4
Harper	0	1	Soiferman	0	1
Hartley	3	3	Sokol	5	4
Hegewald	4	4	Spink <sup>a</sup>	2	2
Hershberger	1	0	St. Pierre <sup>a</sup>	2	1
Hilmi	0	2	Sutherland	2	1
Imam	1	0	Swieskowski	3	4
Incaudo	0	2	Taylor <sup>a</sup>	1	0
Jackson	0	1	Tellier <sup>a</sup>	2	2
Jannetti	19	20	Tiffany	0	1
Jones	4	3	Topkis	2	3
Kahn	1	0	Warren	1	1
Kliner	4	4	Weinstein	2	1
Koser	2	0	White	1	1
Krause	17	18	Wolfe	0	1
Levine	2	1	<b>Total</b>	<b>317</b>	<b>303</b>
<sup>a</sup> Investigator at Canadian site					

Subject enrollment was discontinued at Dr. Feicht's site (Investigator No. 12312) due to irreconcilable data issues and lack of adherence to the study protocol. Because data could not be reconciled against source documents, all efficacy data from this site were disqualified.

## Investigational Plan

### Overall Study Design and Plan - Description

This was a Phase 3, randomized, double-blind, parallel-group multicenter study in ambulatory subjects with AECB. Approximately 110 investigators were to enroll approximately 600 subjects (300 subjects per treatment group). Subjects were randomly assigned in a 1:1 ratio at each investigational site to receive for 7 days either 2 x 500 mg of clarithromycin extended release once a day (QD) plus placebo for clarithromycin immediate release or 500 mg of clarithromycin immediate release twice a day (BID) plus placebo for clarithromycin extended release.

The nature of the study was explained to subjects (and the parents/legal guardians of minor subjects) who presented with clinical signs and symptoms of AECB at Evaluation 1. After informed consent was obtained, a medical history was recorded, and physical examination, vital signs assessment, and laboratory evaluations were performed. A chest x-ray was obtained to exclude subjects with pneumonia, active tuberculosis, or present tumor involving the lung. Female subjects of childbearing potential were required to have a negative urine HCG (human chorionic gonadotropin) pregnancy test prior to enrollment.

Clinical and bacteriological assessments were performed within 48 hours before starting study drug (Evaluation 1). Clinical signs and symptoms of chronic bronchitis were documented, including the subject's baseline (pre-acute episode) condition and current condition. A sputum specimen (by spontaneous expectoration or by transtracheal aspiration) was obtained for Gram stain and culture and susceptibility testing. An acceptable purulent sputum (defined as  $\geq 25$  WBC per field and  $\leq 10$  squamous epithelial cells at 100x magnification) was required for enrollment, although eligible subjects could begin study medication before the results of the sputum culture were known, provided they met the inclusion/exclusion criteria.

Eligible subjects were randomly assigned in a 1:1 ratio to receive either:

clarithromycin extended release tablets 2 x 500 mg QD for 7 days (plus clarithromycin immediate release placebo)	OR	clarithromycin immediate release tablets 500 mg BID for 7 days (plus clarithromycin extended release placebo)
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Subjects returned to the clinic on Study Day 8-10 or within 48 hours after premature discontinuation of study drug (Evaluation 2) and once during Study Days 19 to 21 (Evaluation 3) for clinical and bacteriological assessments. Clinical response was assessed at Evaluation 3 (Test-of-Cure). Safety was evaluated through monitoring of adverse events, laboratory tests, medical history, and physical examination.

The total duration of each subject's participation in the study was approximately 3 to 4 weeks. The total duration of the study from first enrollment to last subject follow-up was approximately 12 months.

Assuming a clinical and bacteriological evaluability rate of 40%, approximately 600 subjects were to be enrolled to obtain 240 clinically and bacteriologically evaluable subjects.

A complete study schematic is presented in the table below:

<b>Study Schematic</b>			
Evaluation Procedure	Evaluation 1 (Within 48 Hours Before Starting Study Drug)	Evaluation 2 (Study Day 8-10 or Within 48 Hours After Early Termination)	Evaluation 3 (Study Day 19-21)
Informed Consent	X		
Pregnancy Test	X&		
Medical History	X		
Complete Physical Examination	X	X	
Vital Signs	X	X	X
Clinical Signs and Symptoms	X	X	X
Clinical Response			X
Chest X-Ray	X	X*	
Gram Stain	X\$	X%	X%
Culture and Susceptibility	X\$	X%	X%
Clinical Laboratory Tests	X	X#	
Compliance Check		X	
Subject Number and Assignment to Treatment Regimen	X		
Dispense Study Drug	X		
Subject Instructions	X		
Monitor Concomitant Medications	X	X	X
Monitor Adverse Events	X	X	X
& If applicable * If clinically indicated \$ Subject must have been producing purulent sputum % If the subject was still producing an acceptable purulent sputum # Clinically significantly abnormal laboratory values detected at this visit were to be followed until they resolved, became stable or became explicable due to a non-therapy problem			

### Discussion of Study Design, Including the Choice of Control Groups

The study was designed as a randomized, double-blind, controlled trial to minimize potential investigator bias. The clarithromycin immediate release formulation was chosen as the comparator because its efficacy and safety have been established in the treatment of AECB. Comparing the clarithromycin extended release formulation to the clarithromycin immediate release formulation should provide an adequate assessment of the clinical and bacteriological efficacy and safety of the extended release formulation of clarithromycin.

The two treatment groups were expected to have comparable efficacy. Assuming bacteriological cure rates for both treatments were approximately 85% (based on Studies M90-418, M90-434, and M90-435, NDA 50-662 [S-004]), 240 clinically evaluable subjects would provide at least 80% power to assure that the lower bound of two-tailed

95% confidence intervals around the difference in response rate remained within -15% or less. A -15% lower bound was chosen based on Issues Regarding Adequacy of Trials, Division of Anti-Infective Drug Products, Point to Consider. Assuming 40% evaluability, approximately 600 subjects were needed.

### **Selection of Study Population**

Male and female subjects at least 12 years of age with a presumptive diagnosis of AECB were eligible for enrollment in this study. Subjects could undergo Evaluation 1 screening procedures 48 hours before the initial dosing; the day of first dosing was designated as Study Day 1.

### **Inclusion Criteria**

The subject had to meet all of the following criteria:

- Ambulatory subjects not requiring IV antibiotic therapy and having a medical history of chronic bronchitis (defined as cough and sputum production for more than 2 consecutive years and on most days in a consecutive 3-month period) and a presumptive clinical diagnosis of AECB supported by appropriate signs and symptoms (i.e., cough, fever, hoarseness, wheezing). Subjects must have had a productive cough with an acceptable purulent sputum, defined as  $\geq 25$  WBC per field and  $\leq 10$  squamous epithelial cells at 100x magnification (low power, 10x objective). Onset of signs and symptoms must have been within 14 days preceding Evaluation 1.
  - Asthmatic subjects, including exercise-induced asthmatics, could be enrolled if their asthma had been stable for at least 6 weeks.
  - Asthmatic subjects who were using inhaled steroid could be enrolled if the amount and frequency of inhaler use were stable.
  - Other inhalation therapy (e.g., non-steroidal anti-inflammatory, bronchodilators, beta adrenergic stimulators, sympathomimetics), regardless if pre-existing, stable, or a new prescription, was allowed.
- Twelve years of age or older.
- A female with childbearing potential could have been enrolled provided she:
  - had a negative urine human chorionic gonadotropin (HCG) pregnancy test (this included subjects with tubal ligation).
  - was using an effective method of birth control. Examples of methods of birth control to prevent pregnancy were:
    - condoms, IUD, contraceptive foams, contraceptive jellies, cervical cap, and
    - oral contraceptives or hormone replacement therapy for a period of 3 months prior to study start until completion of study drug administration.
  - did not attempt to become pregnant during the study period.
- Able to swallow tablets intact.
- The subject had voluntarily signed the informed consent form after the nature of the study had been explained, prior to the performance of any study-related procedure. Subjects between 12 and 18 years of age also required written consent from a parent or legal guardian.

### Exclusion Criteria

Subject were excluded from study participation if they met any of the following criteria:

- History of hypersensitivity or allergic reactions to macrolides.
- Females who were pregnant or lactating.
- Subjects who had:
  - Sinusitis or any other infection requiring systemic antibiotic treatment.
  - Severe or complicated lower respiratory tract infection.
  - Pneumonia (positive chest x-ray at screening).
  - Positive chest x-ray evidence of active tuberculosis, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, pleural effusion or consolidation.
  - Severely compromised respiratory status.
  - Requirement for parenteral antibiotic therapy.
  - Underlying condition/disease that would be likely to interfere with completion of the course or absorption of study drug therapy or follow-up.
  - Known significant renal or hepatic impairment indicated by recent chemistries:
    - serum creatinine > the upper limit of normal for the central laboratory
    - SGOT (AST) >2 X the upper limit of normal
    - SGPT (ALT) >2 X the upper limit of normal
    - alkaline phosphatase > 1.25 X the upper limit of normal
    - total bilirubin >2 X the upper limit of normal
  - Immunocompromised host status or subjects receiving immunosuppressants.
  - Previously had been enrolled in Abbott Studies M97-756 or M97-766.
- Subjects who were currently receiving or who were likely to require any of the following medications during the period between Evaluation 1 (initial presentation to office/clinic) and Evaluation 2 (Study Day 8-10):
  - [redacted] astemizole (Hismanal®), cisapride (Propulsid®), or primozide (Orap®) until 48 hours after last dose of study drug.
  - Concomitant theophylline or any theophylline analog, carbamazepine, ergotamine, dihydroergotamine, triazolam, phenytoin, or hexobarbital unless clinically monitored during the study for signs and symptoms of toxicity.
  - Concomitant warfarin therapy unless prothrombin time could be adequately monitored.
- Subjects who were currently receiving or who were likely to require any of the following medications during the period between Evaluation 1 (initial presentation to office/clinic) and Evaluation 3 (Study Day 19-21):
  - Oral or parenteral steroid at a dose equivalent to 10 mg/day of prednisone.
  - Any immunosuppressant drug.
  - Other systemic antimicrobial therapy.
  - Any other investigational drug.
- Subjects who had taken:
  - A systemic antibiotic within 3 weeks before study drug administration.
  - A long-acting injectable antibiotic (e.g., benzathine penicillin G) within 30 days before study drug administration.
  - An investigational drug within 4 weeks before study drug administration.
- Subjects residing at chronic care facilities.

- Subjects who would require a change in the amount or frequency of use of inhaled steroid medications.

### **Removal of Subjects from Therapy or Assessment**

If study drug therapy was prematurely discontinued or the subject withdrew from the study after completing study drug but prior to the completion of all study procedures, the primary reason for discontinuation was to be recorded on the appropriate CRF.

A subject was withdrawn from the study immediately if any of the following occurred:

- Clinically significant deterioration of the subject's medical status.
- Subject's response to therapy was unsatisfactory (>72 hours after start of treatment):
  - Persistence of pyrexia, increase or no trend to decline.
  - Persistence or worsening of clinical symptoms and/or respiratory status.
  - Chest radiographs indicated worsening pulmonary status, i.e., development of pneumonia.
- Pretreatment laboratory result was clinically significantly abnormal.
- The investigator decided that discontinuation was in the best interest of the subject.
- The subject or parent/legal guardian requested withdrawal from the study.
- Selection criteria were violated after the subject started study drug.

A subject who was prematurely withdrawn from study drug was instructed to return to the investigator's office within 48 hours of the last dose of study drug for completion of Evaluation 2 procedures. A clinical evaluation was to be performed and a sputum sample for culture (if the subject was still producing sputum) was to be obtained. The Evaluation 2 procedures were to be completed prior to the institution of another antibiotic or other appropriate therapy, but were not in any way to delay institution of any new treatments or therapeutic modalities which, in the investigator's opinion, were necessary.

If the subject discontinued from the study after the full course of therapy, but prior to the completion of all study procedures, sputum samples for culture (if the subject was still producing sputum) were to be obtained if possible.

### **Treatments Administered**

Treatment assignment was determined by the randomization schedule such that equal numbers of subjects were assigned to each of the two treatment regimens. Subjects received either 2 x 500 mg (two 500-mg tablets) of clarithromycin extended release QD (and immediate release placebo) or a 500 mg tablet of clarithromycin immediate release BID (and extended release placebo). The duration of therapy was 7 days. The medication was to be taken under fed conditions.

All study medication was to be stored at controlled room temperature (20-25° C) and protected from light. Clarithromycin extended release (or corresponding placebo) and clarithromycin immediate release (or corresponding placebo) were packaged in labeled bottles containing a sufficient supply for a 7-day course of therapy. The labels affixed to each of the bottles included the subject number, study number, number of tablets in the bottle, directions for administration, and spaces to record the subject's initials and dispensing date. The investigator or study coordinator dispensed study drug in ascending numerical sequence as subjects were enrolled in the study in order to preserve the integrity of the randomization schedule. When the investigator or study coordinator

dispensed the medication, he/she was to record the subject's initials and date dispensed on the labels and on the drug dispensing log.

The investigator or designee agreed not to supply study drugs to any subject not enrolled in this study, or to any physician or scientist not named as subinvestigator.

### **Prior and Concomitant Therapy**

Any medications (including over-the-counter medication) taken by the subject within the 4 weeks prior to study start were to be recorded on the appropriate CRF along with dosage information, dates of administration, and reason for use. This included any medications used for previous episodes of AECB within that time frame.

Because of the potential interaction with clarithromycin, subjects were not allowed to take [redacted] astemizole, cisapride, or pimozide while on study medication. For the same reason, subjects were not allowed to take theophylline or any theophylline analog, carbamazepine, ergotamine, dihydroergotamine, triazolam, phenytoin, or [redacted] unless the subject was clinically monitored for signs and symptoms of toxicity. While on study medication, subjects were also not allowed to take concomitant warfarin therapy unless prothrombin time could be adequately monitored.

Subjects were not to receive any oral or parenteral steroids at a dose equivalent to 10 mg/day of prednisone, any immunosuppressant drug, other systemic antimicrobial therapy, or other investigational agent until after Evaluation 3. If the administration of any concurrent medication was necessary during the course of this study, dosage information, dates of administration, and indication for use were to be reported on the CRF. In the event that any surgical or diagnostic procedure (other than those described in the protocol) was performed during the course of the study, the date, time, and description of the procedure(s), as well as all perioperative medications and anesthetics and clinical findings were to be recorded on the CRF.

### **Treatment Compliance**

In order to document compliance with the treatment regimen, subjects were instructed to return the bottles of medication (even if empty) to the study coordinator at Evaluation 2. The study drug bottles were retained by the study coordinator at Evaluation 2 for both treatment groups. Compliance with each study medication was to be documented by the study coordinator on the appropriate CRF. The exact start and stop date, the number of tablets taken, and the number of tablets remaining were to be recorded on the CRF. If the number of tablets taken and the number of tablets returned did not add up to the number of tablets dispensed, an explanation was to be provided on the CRF.

An overall accountability of study medication was to be performed and verified by the Abbott monitor or designee throughout the study and at the site close-out visit.

## Efficacy and Safety Variables

### Efficacy and Safety Measurements Assessed

Cultures for isolation of pathogens from purulent sputum were to be obtained at Evaluation 1 to identify the presence of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and other pathogens. Cultures were also to be obtained at Evaluations 2 and/or 3 for bacteriological analysis (if the subject was still producing purulent sputum at the time of subsequent Evaluation visits). Clinical assessments of the signs and symptoms of AECB were performed at Evaluations 1, 2 and 3, and a clinical response to therapy was assessed by the investigator at Evaluation 3 (Test-of-Cure Visit).

Adverse events and concomitant medications were to be monitored throughout the study. A complete physical examination with vital signs was to be performed at Evaluations 1 and 2, and vital signs were also assessed at Evaluation 3. Any clinically abnormal observations arising during the study treatment period were followed to a satisfactory resolution. Hematology and serum chemistry tests were performed at Evaluations 1 and 2.

### Efficacy Procedures

Efficacy in this study was assessed by clinical resolution of signs and symptoms of AECB and bacteriological eradication of pathogens.

Sputum samples for Gram stain and culture and susceptibility testing were obtained at pretreatment (Evaluation 1) and at Evaluations 2 and 3 (if the subject was still producing purulent sputum). Sputum samples were to be obtained by either spontaneous or induced expectoration or by transtracheal aspiration. If induced expectoration was utilized for obtaining a sputum sample, only normal saline without preservative was to be used as the vehicle; bacteriostatic vehicles were not permitted.

### Gram Stain

From the sputum sample, the investigator prepared four sputum smears that were air-dried for Gram stain evaluation. Each slide was clearly identified with the study number, subject number, subject initials, and date the specimen was obtained. Two slides were stained, one of which was retained by the site. One Gram-stained slide (which was used to determine acceptability) and the two unstained slides were sent to [redacted] Routine culture analysis, as well as susceptibility testing for *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and other pathogens was performed on all sputum samples.

### Culture and Susceptibility Testing

The central laboratory specifically identified the pathogens as to genus and species. *In vitro* susceptibility to clarithromycin was determined by National Committee for Clinical Laboratory Standards (NCCLS) methods and interpretive criteria were strictly followed. The disk-diffusion method, with measurement of the zone of inhibition in millimeters (mm), and/or the dilution method, with measurement of the minimum inhibitory concentrations (MIC) in micrograms per milliliter ( $\mu\text{g/mL}$ ), were used to determine susceptibility. Susceptibility was recorded as susceptible, intermediate or resistant as shown in the table below:

Susceptibility Criteria to Clarithromycin						
Pathogen	Minimum Inhibitory Concentration ( $\mu\text{g/mL}$ )			Zone Diameter (mm)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
<i>H. influenzae</i>	$\leq 8$	16	$\geq 32$	$\geq 13$	11-12	$\leq 10$
<i>S. pneumoniae</i>	$\leq 0.25$	0.5	$\geq 1$	$\geq 21$	17-20	$\leq 16$
<i>M. catarrhalis</i> <sup>®</sup>	$\leq 2$	4	$\geq 8$	$\geq 18$	14-17	$\leq 13$
<i>H. parainfluenzae</i>	$\leq 8$	16	$\geq 32$	$\geq 13$	11-12	10
<i>S. aureus</i>	$\leq 2$	4	$\geq 8$	$\geq 18$	14-17	13

<sup>®</sup> *S. aureus* breakpoints were used for *M. catarrhalis*.

### Clinical Signs and Symptoms

The investigator assessed the subject's baseline condition (pre-acute episode) of chronic bronchitis as indicated in the table below:

Assessment of Baseline (Pre-Acute) Clinical Signs and Symptoms	
Clinical Sign/Symptom	Assessment
Cough	Absent mild: does not interfere with normal activities moderate: interferes with normal activities or sleep severe: causes chest pain and dizziness
Sputum Production	absent, mild, moderate, severe
Sputum Production Volume (in the last 24 hours)	<1 oz; 1-2 oz, 2-3 oz, >3 oz
Dyspnea	Absent mild: not enough to interfere with normal activities moderate: interferes with normal activities to some degree severe: prevents normal activities
Fever ( $\geq 100^\circ\text{F}$ or $\geq 37.8^\circ\text{C}$ )	absent, present

Clinical signs and symptoms of the subject's current episode of AECB were assessed at Evaluations 1, 2, and 3, with a clinical response to therapy assessed by the investigator at Evaluation 3 (Test-of-Cure Visit). The assessment categories for each clinical sign and symptom are presented in the table below:

Assessment of Clinical Signs and Symptoms of Current Episode of AECB	
Clinical Sign/Symptom	Assessment
Cough	Absent mild: does not interfere with normal activities moderate: interferes with normal activities or sleep severe: causes chest pain and dizziness
Sputum Production	absent*, mild, moderate, severe
Sputum Production Volume (in the last 24 hours)	<1 oz, 1-2 oz, 2-3 oz, >3 oz
Sputum Appearance	Purulent Absent: None* Purulent Present: Almost uniform yellow or green thick opaque material with the appearance of pus Hemoptic Absent: No blood-stained material Hemoptic Present: Blood-stained material
Dyspnea	Absent mild: not enough to interfere with normal activities moderate: interferes with normal activities to some degree severe: prevents normal activities
Rales/Crackling	absent, present
Egophony	absent, present
Rigors	absent, present
Ronchi/Wheezing	absent, present
Substernal Pain	absent, present
Pleuritic Pain	absent, present
Pleural Effusion	absent, present
Fever ( $\geq 100^{\circ}$ F or $\geq 37.8^{\circ}$ C)	absent, present
Headache	absent, present
Coryza	absent, present
Hoarseness	absent, present
Sore Throat	absent, present
* Subjects had to be producing purulent sputum at Evaluation 1 to be eligible for enrollment	

### Safety Procedures

The safety of the study medication was monitored throughout the study by physical examinations, including vital signs, concomitant medications, the assessment of adverse events, and laboratory evaluations. Physical examinations and laboratory evaluations were performed prior to treatment (Evaluation 1) to assess the subject's medical status at baseline and at Evaluation 2 or within 48 hours posttreatment (if prematurely discontinued from study drug); chest x-ray was performed at Evaluation 1 and, if clinically indicated, also at Evaluation 2. Subjects were instructed to contact the investigator or return to the study site at any time during the treatment period if they felt their condition had not improved or if signs and symptoms of infection worsened.

### Laboratory Procedures

Laboratory evaluations (hematology and serum chemistry) were performed by [redacted] [redacted] This laboratory is accredited by the College of American Pathologists (CAP). All blood samples were collected in accordance with accepted laboratory procedures. Specimens were obtained at Evaluations 1 and 2 for the following tests listed in the table below:

Clinical Laboratory Tests	
Hematology Tests	Serum Chemistry Tests
Hemoglobin	Blood Urea Nitrogen (BUN)
Hematocrit	Creatinine
White Blood Cell Count (WBC) with Differential	Total Bilirubin
Platelet Count	AST/SGOT
	ALT/SGPT
	Alkaline Phosphatase

If an unexpected laboratory value(s) outside the normal range occurred, the investigator repeated the laboratory test(s) as judged appropriate to ensure the validity of the abnormal result(s). Liver and renal function test(s) were to be repeated if one or more of the following was observed:

- SGOT (AST) >2 X the upper limit of normal;
- SGPT (ALT) >2 X the upper limit of normal;
- Alkaline phosphatase >1.25 X the upper limit of normal;
- Creatinine > upper limit of normal for the central laboratory (if, in the investigator's opinion, the creatinine was elevated due to pretreatment dehydration, the serum creatinine could have been repeated after rehydration of the subject);
- Total bilirubin >2 X the upper limit of normal (total bilirubin was to be repeated and direct bilirubin was also performed)

If test results were not within the limits specified upon repeat testing, the subject could be continued in the study only at the discretion of the investigator with concurrence of the sponsor.

Any significantly abnormal laboratory result was to be followed until it resolved, stabilized, or became explainable due to other known causes (i.e., concurrent condition or medication) and clinical judgment indicated that further studies were not warranted. The investigator assessed the etiology of any significantly abnormal results. Clinically significant abnormal laboratory results that were considered to be adverse events were also recorded on the adverse events CRF.

### **Other Drug Levels**

Subjects who were receiving theophylline, a theophylline analog, or other allowed drug(s) were clinically monitored for signs and symptoms of toxicity. Since this was medical practice and not part of this study, the levels were not reported.

### **Pregnancy Test**

If a subject was female and of childbearing potential (postmenopausal for less than 1 year or had not had a hysterectomy), a negative urine HCG pregnancy test result was required within 2 days prior to enrollment.

### **Nonlaboratory Procedures**

#### **Medical History**

A complete medical history was obtained at pretreatment (Evaluation 1 ) including:

- duration of signs and symptoms of this infection
- any prior medical evaluation for this infection
- any prior medical treatment (prescription drug) for this infection
- any underlying pulmonary or other clinically significant medical conditions
- history of chronic bronchitis or other pulmonary diseases (including hospitalizations)
- concurrent illnesses
- concomitant and recent medications including asthma medications such as bronchodilators, theophylline, and steroids (both oral and inhaled)
- smoking habits

#### **Physical Examination**

A complete physical examination was performed at Evaluations 1 and 2, including the following vital signs assessments:

- blood pressure (after sitting 3 minutes)
- pulse (30 seconds)
- respiration rate
- body temperature
- height (Evaluation 1 only) and weight

A genitourinary examination was optional. Only vital signs were measured at Evaluation 3.

#### **Chest X-ray**

A posterior-anterior (PA) chest x-ray was obtained prior to initiation of therapy at Evaluation 1 to exclude subjects with pneumonia, active tuberculosis, or present tumor involving the lung. The investigator compared the results of this pretreatment x-ray to any pre-screening chest x-rays obtained within the past year, if available. Chest x-rays could also be obtained at Evaluation 2, if clinically indicated. If the radiograph from

Evaluation 2 demonstrated acute infiltrates, the subject was considered a treatment failure. X-ray interpretations by the investigator were accepted.

### Adverse Events

Adverse events were defined as any unexpected event(s) such as sign(s), symptom(s), and/or laboratory finding(s) associated with the use of drugs in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject, occurring between the start of the study through the post-therapy visit (Evaluation 3).

Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken. The investigator assessed any adverse event and recorded information in detail onto the adverse event section of the CRF. The report of the adverse event included the date and time of onset, description, severity, date of resolution (or duration of event if <24 hours), unifying diagnosis/syndrome (if known), etiology, investigator's assessment of relationship to the study drug, any actions taken, and whether or not the adverse event met the criteria for a serious adverse event. Any adverse events or abnormal laboratory results that were considered clinically significant were followed to a satisfactory resolution.

The investigator used the following definitions to rate the severity of each adverse event:

<u>Mild</u>	The adverse event was transient and easily tolerated by the subject.
<u>Moderate</u>	The adverse event caused the subject discomfort and interrupted the subject's usual activities.
<u>Severe</u>	The adverse event caused considerable interference with the subject's usual activities and could have been incapacitating or life-threatening.

The possible relationship of the adverse event to the study drug was assessed using the following definitions:

<u>Probable</u>	An adverse event had a strong temporal relationship to study drug or recurred on rechallenge and another etiology was unlikely or significantly less likely.
<u>Possible</u>	An adverse event had a strong temporal relationship to study drug and an alternative etiology was equally or less likely compared to the potential relationship to study drug.
<u>Probably Not</u>	An adverse event had little or no temporal relationship to the study drug and/or a more likely alternative etiology existed.
<u>Not Related</u>	An adverse event was due to an underlying or concurrent illness or effect of another drug and was not related to the study drug (e.g., had no temporal relationship to study drug or had a much more likely alternative etiology).

### Serious Adverse Events

Any adverse event that resulted in any of the criteria listed in the table below was considered a serious adverse event (SAE):

<b>Criteria for a Serious Adverse Event</b>	
<b>If the Adverse Event:</b>	
	Resulted in a Persistent or Significant Disability/Incapacity
	Resulted in a Congenital Anomaly
	Resulted in a Hospitalization
	Resulted in Prolongation of Hospitalization
	Required Medical or Surgical Intervention to Prevent Serious
<b>Outcome</b>	
	Was a Life-Threatening Situation (defined as the subject being at immediate risk of death from the event as it occurred)
	Resulted in the Death of the Subject

A serious adverse event (SAE) included any adverse drug experience occurring at any dose that resulted in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not have resulted in death, been life-threatening or required hospitalization could have been considered serious when, based upon appropriate medical judgment, they jeopardized the subject and could have required medical or surgical intervention to prevent one of the outcomes listed above, i.e., death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

If a study subject had a miscarriage/spontaneous abortion or had an elective abortion during the study, this event was also to be reported as an SAE.

#### **Deaths**

Any death that occurred during the study or within 30 days of discontinuation from the study was to be reported as a serious adverse event. Copies of the death certificate and autopsy report were to be submitted when available.

#### **Efficacy Variables**

##### **Primary Variables**

The primary efficacy variables for this study were the clinical cure rate, the subject bacteriological cure rate, and the pathogen eradication rate, as described in the table below:

Definitions of Primary Efficacy Variables for Analysis	
Response Variable	Definition
The Clinical Cure Rate	The percentage of subjects who had a clinical response of "Cure."
The Subject Bacteriologic Cure Rate	The percentage of bacteriologically evaluable subjects (i.e., subject with at least one evaluable pathogen at Evaluation 1) who demonstrated eradication of all evaluable pathogens.
The Pathogen Eradication Rate	Two definitions were examined: 1) for each pretreatment pathogen, the percent of subjects in whom the pathogen was eradicated; 2) the percentage of all evaluable pretreatment pathogens eradicated (regardless of number of subjects).

**Clinical Response Definitions**

The investigator compared the clinical findings at Evaluation 3 to the findings prior to study treatment for each subject and assigned a clinical response. Bacteriological results were not considered when assigning clinical response. The clinical response was rated using the following definitions:

- Clinical Cure (Evaluation 3 only) Acute signs and symptoms of AECB had resolved or improved to a baseline level (pre-acute level) without the need for additional antimicrobial therapy.
- Clinical Failure (Evaluation 2 and Evaluation 3 or at premature discontinuation) Continuation or worsening of the signs and symptoms of AECB above the baseline level at Evaluation 2 or 3, or at the time of discontinuation of study medication, and further antimicrobial therapy was warranted.
- Indeterminate (Evaluation 3 only) The evaluation was not possible (e.g., disallowed medication used, no follow-up examination); the reason was documented on the CRF.

**Bacteriological Response Definitions**

The bacteriological response(s) was assigned by Abbott Laboratories for each valid pretreatment pathogen by comparing the culture results at Evaluation 2 and Evaluation 3 (or at the time of premature discontinuation) with results from Evaluation 1. The response categories were as follows:

Presumed Eradication : In the absence of a repeat sputum culture, the subject was considered a presumed eradication if the definition of clinical cure was met.

<u>Eradication</u>	The absence of the entry pathogen(s) from a repeat sputum culture performed at Evaluations 2 and 3.
<u>Presumed Persistence</u>	In the absence of a repeat sputum culture, the initial pathogen(s) was presumed persistent if the definition of clinical failure was met.
<u>Persistence</u>	The presence of the original pathogen(s) at Evaluation 2 or Evaluation 3 culture(s) or at the time of discontinuation of study therapy.
<u>Superinfection</u>	Presence of a new pathogen(s) in Evaluation 2 or Evaluation 3 culture in a symptomatic subject.
<u>Indeterminate</u>	The evaluation was not possible (e.g., subject did not return).

### **Secondary Variable**

The secondary efficacy variable was the change from baseline in clinical signs and symptoms.

### **Drug Concentration Measurements**

Drug concentration measurements for the study medications were not performed for this study.

### **Statistical Methods Planned in the Protocol and Determination of Sample Size**

#### **Statistical and Analytical Plans**

- All statistical tests were two-tailed with the significance level of 0.05. All p-values were rounded to three decimal places.

#### **Demographic and Other Baseline Characteristics**

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the two treatment groups provided by randomization. Quantitative variables, such as age and other pertinent baseline characteristics, were analyzed by a one-way analysis of variance (ANOVA), while categorical variables, such as gender, race and other pertinent baseline characteristics, were analyzed by Fisher's exact test or its extension to RxC tables.

#### **Efficacy Analyses**

The primary efficacy variables were the clinical cure rate, the subject bacteriological cure rate, and the pathogen eradication rate; the secondary efficacy variable was the change in clinical signs and symptoms. The efficacy variables were analyzed using Fisher's exact test comparing the two treatment groups. Binomial 95% confidence intervals, based on

normal approximation for the binomial distribution, were computed for the difference of the above rates (clarithromycin extended release - clarithromycin immediate release) between the treatment groups.

In addition, the efficacy variables were summarized by treatment group according to subgroups such as gender, race, age, tobacco use, and other pertinent factors. Treatment groups were further compared using the Cochran-Mantel-Haenszel test with stratifications by the above variables and by investigator sites. The individual pathogen eradication rate was not analyzed by stratification due to sparseness. Treatment by investigator sites interaction was also examined; sites with very small numbers of subjects could be combined by regions, as appropriate.

Changes from Evaluation 1 (pretreatment) to Evaluations 2 and 3 in each clinical sign and symptom were summarized by treatment group. The two treatment groups were compared with respect to the percentage of subjects who showed either resolution or improvement in the sign and symptom among the subjects presenting with the sign and symptom. The analysis was performed using Fisher's exact test.

If clinical response and bacteriological response could not be determined due to any reason (for example, missing visits), these subjects were treated as failures in the intent-to-treat data set analyses and were excluded from the evaluable data set analyses.

### **Safety Analyses**

Subjects who took at least one dose of study drug were included in the safety analyses.

### **Adverse Events**

All treatment-emergent adverse events (i.e., those that began or worsened in severity after randomized drug was administered) were mapped to the COSTART III dictionary.<sup>5</sup>

Subjects reporting more than one adverse event for a particular COSTART term were counted only once for that term using the most severe incident. If more than one type of event occurred within a body system for a subject, the subject was counted only once when summarizing by body system. Adverse event incidence rates, including and excluding events with no relationship to study drugs, were summarized by treatment group and compared using Fisher's exact test. In addition, serious adverse events and discontinuations due to adverse events were summarized by treatment group.

### **Laboratory Data**

Clinical laboratory data were collected at Evaluations 1 and 2. Results were listed for each subject and values outside the laboratory reference range were identified.

Potentially clinically significant laboratory values were summarized within each treatment group.

### **Vital Signs**

Mean changes from baseline in vital signs data were summarized within each treatment group. No formal statistical tests were performed.

## Disposition of Subjects

Six hundred twenty (620) subjects were randomized in the study and took study drug; 317 subjects took clarithromycin extended release (ER) tablets and 303 subjects took clarithromycin immediate release (IR) tablets. Seven additional subjects were enrolled, three into the clarithromycin ER group and four into the clarithromycin IR group; one subject was discontinued due to selection criteria violation (allergy to macrolide antibiotics) and six subjects received study drug but did not return for any evaluations after the pretreatment assessment. These seven subjects were 4154, 4156, 4157, and 4159 from Dewan (Investigator No. 9624), 3987 and 4234 from Dotson (Investigator No. 13533), and 3309 from Fox (Investigator No. 13647). There was no evidence that these seven subjects took any study drug; hence, they were excluded from all analyses but are included in the data listings.

Overall, 17% (107/620) of the treated subjects prematurely discontinued from the study; 19% (61/317) of subjects discontinued from study in the clarithromycin ER group and 15% (46/303) of subjects discontinued from study in the clarithromycin IR group. The most frequent reason for withdrawal from study in both groups was insufficient improvement, cited by 5% (17/317) of subjects in the clarithromycin ER group and 4% (13/303) of subjects in the clarithromycin IR group. Additional reasons for premature discontinuation from study in the clarithromycin ER and clarithromycin IR groups included adverse event (11 subjects and nine subjects, respectively), lost to follow-up (eight subjects and four subjects, respectively), selection criteria violated after enrollment (six subjects and four subjects, respectively), did not meet entrance criteria (four subjects in each treatment group), investigator request (three subjects and five subjects, respectively), subject noncompliance (one subject and three subjects, respectively), and "other" reasons (eight subjects and four subjects, respectively); in addition, three subjects in the clarithromycin ER group requested discontinuation.

Overall, 7% (43/620) of the subjects prematurely discontinued treatment; 7% of subjects discontinued study drug in both the clarithromycin ER (23/317) and clarithromycin IR (20/303) groups. The most frequent reason for discontinuing study drug was adverse event, cited by 3% of subjects in both the clarithromycin ER (9/317) and clarithromycin IR (9/303) groups. Additional reasons for prematurely discontinuing study drug by subjects in the clarithromycin ER and clarithromycin IR groups included selection criteria violated after enrollment (four subjects and three subjects, respectively), insufficient improvement (two subjects and four subjects, respectively), did not meet entrance criteria (three subjects and two subjects, respectively), and "other" reasons (four subjects and one subject, respectively); in addition, one subject in the clarithromycin ER group requested discontinuation of study drug and one subject in the clarithromycin IR group discontinued study drug due to noncompliance. The details of the subjects who prematurely discontinued study drug are presented by treatment group in the table below:

Subjects Whose Treatment Was Prematurely Discontinued					
<u>Primary Reason for Discontinuation</u>	<u>Subject #</u>	<u>Age (years)</u>	<u>Sex</u>	<u>Days on Therapy</u>	<u>Investigator</u>
<b>Clarithromycin ER Group</b>					
Adverse Event	4253	65	F	3	Allen
	4231	73	M	3	Dotson
	3227	52	F	5	Jannetti
	3122	41	F	6	Mansfield
	3170	70	F	4	Miller
	3708	67	M	1	Moriarty
	3268	73	F	5	Nayak
	4074	51	M	3	Siami
	3373	59	F	3	Weinstein
Selection Criteria Violated After Enrollment	3134	37	F	5	Arno
	3996	60	F	1	Jannetti
	4101	40	M	2	Jannetti
	4118	31	F	7	Singh
Insufficient Improvement	4116	78	M	3	Brazinsky
	3222	58	F	6	Jannetti
Did Not Meet Entrance Criteria	3869	71	M	1	Bruya
	3969	51	M	3	Chiambretti
	3794	84	M	4	Hegewald
Other	4158 <sup>a</sup>	49	M	5	Dewan
	4058 <sup>b</sup>	78	M	2	Krause
	5105 <sup>b</sup>	45	M	3	McCarty
	3444 <sup>b</sup>	52	F	1	Munk
Subject Request	5045	65	F	1	Onuska
<b>Clarithromycin IR Group</b>					
Adverse Event	3690	63	M	2	Cutler
	3287	53	F	1	Fisher
	3306	54	F	5	Gellrick
	3790	72	M	4	Hegewald
	3762	71	M	2	Kliner
	3931	76	M	6	Miller
	4197	69	M	1	Moriarty
	4071	49	F	2	Munk
	3267	57	F	3	Nayak
Selection Criteria Violated After Enrollment	3979	25	M	6	Dewan
	4142	40	M	5	Dewan
	3221	88	M	3	Jannetti
<p>a Subject's study drug was stolen.</p> <p>b Exclusionary laboratory results at Evaluation 1.</p>					

<b>Subjects Whose Treatment Was Prematurely Discontinued (Continued)</b>					
<u>Primary Reason for Discontinuation</u>	<u>Subject #</u>	<u>Age (years)</u>	<u>Sex</u>	<u>Days on Therapy</u>	<u>Investigator</u>
Insufficient Improvement	3835	83	F	7	Brazinsky
	3884	51	F	6	Dewan
	4152	53	F	7	Dewan
	3121	76	F	3	Mansfield
Did Not Meet Entrance Criteria	3141	70	M	6	Incaudo
	3696	74	F	1	Schenkel
Other	4214 <sup>b</sup>	63	F	Unknown	Bensch
Subject Noncompliance	3647	62	F	8	Bensch

a Subject's study drug was stolen.  
 b Exclusionary laboratory results at Evaluation 1.

### Protocol Deviations

In reviewing the data for all subjects, variations from the protocol were identified. Commonly reported variations included mistiming of a visit or procedure, mistiming of doses, and selection criteria deviations. Some subjects were excluded from the bacteriological and clinical efficacy analyses, the clinical efficacy analyses, and/or the intent-to-treat analyses due to protocol variations. Due to irreconcilable data issues and lack of adherence to study protocol, Abbott discontinued subject enrollment at Dr. Feicht's site. The data could not be reconciled against the source documents; thus, the efficacy data were disqualified. None of the variations noted at any investigational site compromised the safety analyses.

### Efficacy Evaluation

#### Data Sets Analyzed

Four data sets were analyzed. A "clinically and bacteriologically evaluable" subject population, a "clinically evaluable" (clinical outcomes only) subject population, and an intent-to-treat subject population were analyzed for efficacy. An "all treated subjects" population was analyzed for safety. Subjects were classified to each of the populations before unblinding.

#### Clinically Evaluable Subject Population

All of the following criteria were to have been satisfied for a subject to be considered clinically evaluable:

- The subject had taken study drug for a minimum of 3 full days to qualify for efficacy evaluation as a clinical failure; to qualify as a clinical cure, the subject had taken at least 80% of prescribed study medication.
- The subject did not receive any other antimicrobial agent during the period 21 days prior to the start of study drug through the subject's final clinical visit unless the