- The subject returned for Evaluation 4 (Study day 21-28) or the subject was considered a treatment failure before Evaluation 4.
- A clinical evaluation was conducted at Evaluation 4 (study day 21-28) or the subject was a treatment failure before Evaluation 4.

Clinically and Bacteriologically Evaluable Subject Population

In addition to the above conditions, subjects must have had an acceptable pretreatment gram stain (<10 squamous epithelial cells and >25 polymorphonucleated leukocytes per low power field) and at least one target pathogen (*H. influenzae*, *H. parainfluenzae*, *S. aureus*, *L. pneumophila*, *S. pneumoniae*, or *M. catarrhalis*) was isolated from the pretreatment culture or at least one target pathogen (*M. pneumoniae*, *C. pneumoniae*, or *L. pneumophila*) was identified via serology or antigen testing.

Intent-to-Treat Subject Population

All subjects who took at least one dose of study drug and had a clinical diagnosis of CAP confirmed by a positive pretreatment chest x-ray 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

Ninety-five (95) subjects were randomized to and took clarithromycin IR and 86 were randomized to and took trovafloxacin. Thirty subjects (10 clarithromycin IR and 20 trovafloxacin) were excluded from the clinically evaluable analyses.
Eleven subjects were excluded because they did not return for the Test-of-Cure Visit, eight returned for the Test-of-Cure Visit outside the allowable window, four subjects used confounding medication, three subjects did not have a chest x-ray performed at the Test-of-Cure Visit, two subjects did not meet the selection criteria, and two subjects had confounding illness.
Ninety-seven subjects (41 clarithromycin IR and 56 trovafloxacin) were excluded from the clinical and bacteriological evaluable analyses of efficacy. Of these, 77 (35 clarithromycin IR and 42 trovafloxacin) subjects did not have a target pathogen isolated at pretreatment. Of the remaining 20 subjects who were excluded, eight subjects did not return for the Test-of-Cure Visit, three subjects returned for the Test-of-Cure Visit outside the allowable window, three subjects had an unacceptable gram stain at pretreatment, two subjects did not meet the selection criteria due to abnormal pretreatment laboratory values, two subjects used confounding medications, one subject

had a confounding illness, and one subject did not have a chest x-ray performed at the Test-of-Cure Visit. 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.
No subject was excluded from the Intent-to-Treat efficacy analyses.
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		
	Clarithromycin IR	Trovafloxacin
Total Randomized	95	86
Total Took Study Medication (All-Treated Subjects Population)	95	86
Intent-to-Treat Analyses	95	86
Clinically Evaluable Analyses	85	66
Excluded from the Clinically Evaluable Analyses	10	20
Subject did not return for Test-of-Cure Visit	3	8
Mistiming of Test-of-Cure Visit	2	6
Used confounding medication	1	3
Chest x-ray was not performed at the Test-of-Cure Visit	0	3
Selection criteria not met (abnormal pretreatment laboratory values)	2	0
Confounding Illness	2	0
Clinically and Bacteriologically Evaluable Analyses	54	30
Excluded from the Clinically and Bacteriologically Evaluable Analyses[a]	41	56
No target pathogen isolated pretreatment	35	42
Subject did not return for Test-of-Cure Visit	2	6
Mistiming of Test-of-Cure Visit	1	2
Pretreatment Gram stain unacceptable	0	3
Selection criteria not met (abnormal pretreatment laboratory values)	2	0
Used confounding medication	0	2
Confounding illness	1	0
Chest x-ray was not performed at the Test-of-Cure Visit	0	1

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

Demographic and Other Baseline Characteristics

Demographics

There were no statistically significant differences between the treatment groups in sex, race, age, or weight in any subject population. The majority of the subjects were female (52%) and white (89%). The mean age of all subjects was 48.3 years, and age ranged from 18 to 80 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 IR	Trovafloxacin	
Total Treated	95	86	
Sex			>0.999
Female	50 (53%)	45 (52%)	
Male	45 (47%)	41 (48%)	
Race[b]			0.818
White	85 (89%)	76 (88%)	
Black	5 (5%)	7 (8%)	
Other	5 (5%)	3 (3%)	
Age (years)			0.407
<40	24 (25%)	32 (37%)	
40-64	52 (55%)	38 (44%)	
≥65	19 (20%)	16 (19%)	
Mean (SD)	49.1 (13.8)	47.3 (16.1)	
Range	18 - 76	19 - 80	
Weight (kg)			0.246
<45	0 (0%)	1 (1%)	
45 - <70	29 (31%)	21 (24%)	
≥70	66 (69%)	63 (73%)	
No data	0 (0%)	1 (1%)	
Mean (SD)	81.9 (18.7)	85.3 (20.6)	
Range	48 - 154	43 - 159	

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

There were no statistically significant differences between treatment groups in presenting conditions, medical history, and social history in any subject population. The table below summarizes the presenting conditions, medical history, and social history for All-Treated Subjects.

Summary of Presenting Conditions, Medical History, and Social History (All-Treated Subjects Population)

Characteristic	Number of Subjects by Treatment Group				P-value[a]
	Clarithromycin IR		Trovafloxacin		
Total Treated	95		86		
Diseases/Conditions Present					Not computed
Surgical History	71	(75%)	68	(79%)	
Respiratory Disease	58	(61%)	57	(66%)	
Musculoskeletal	50	(53%)	57	(66%)	
Head-Eyes-Ears-Nose-Throat	50	(53%)	47	(55%)	
Cardiovascular	51	(54%)	40	(47%)	
Gastrointestinal	43	(45%)	39	(45%)	
Neurologic	43	(45%)	32	(37%)	
Drug Allergy	36	(38%)	27	(31%)	
Endocrine Disorder	27	(28%)	28	(33%)	
Non-Drug Allergy	20	(21%)	21	(24%)	
Renal Disease	11	(12%)	13	(15%)	
Cancer	12	(13%)	5	(6%)	
Occup./Environmental Hazard Exposure	3	(3%)	9	(10%)	
Immunodeficiency	5	(5%)	5	(6%)	
Hepatic Disease	4	(4%)	4	(5%)	
Drug/Alcohol Abuse	3	(3%)	3	(3%)	
Pulmonary Disease History					Not computed
Community-Acquired Pneumonia	95	(100%)	86	(100%)	
Acute Bronchitis	30	(32%)	26	(30%)	
Bronchial Asthma	20	(21%)	13	(15%)	
Chronic Bronchitis	11	(12%)	8	(9%)	
COPD	12	(13%)	6	(7%)	
Lung Abscess	0	(0%)	1	(1%)	
Overall Clinical Condition					0.547
Good	35	(37%)	28	(33%)	
Fair	60	(63%)	58	(67%)	
Infection Status					0.984
Mild	20	(21%)	18	(21%)	
Moderate	75	(79%)	68	(79%)	
Prior Medical Evaluation for Current Infection					0.881
Yes	14	(15%)	12	(14%)	
No	81	(85%)	74	(86%)	
Prior Medical Treatment for Current Infection					0.598
Yes	39	(41%)	32	(37%)	
No	56	(59%)	54	(63%)	

a P-values are from Fisher's exact test for tobacco use and alcohol consumption, from Cochran-Mantel-Haenszel for overall clinical condition, infection status, prior medical evaluation and prior medical treatment, and from ANOVA for number of LRTI infections within past 12 months.

Summary of Presenting Conditions, Medical History, and Social History (All-Treated Subjects Population) (Continued)

Characteristic	Number of Subjects by Treatment Group				P-value[a]
	Clarithromycin IR		Trovafloxacin		
Number of LRTI Infections in Past 12 Months					0.430
1	77	(81%)	68	(79%)	
2	15	(16%)	14	(16%)	
≥3	3	(3%)	4	(5%)	
Mean (SD)	1.2	(0.6)	1.3	(0.8)	
Range	[redacted]				
Tobacco Use[b]					0.339
Non-Tobacco User	27	(28%)	31	(36%)	
Ex-Tobacco User	27	(28%)	18	(21%)	
Tobacco User	41	(43%)	37	(43%)	
Alcohol Consumption[c]					0.054
Non-Drinker	38	(40%)	47	(55%)	
Ex-Drinker	7	(7%)	4	(5%)	
Occasional Drinker	37	(39%)	24	(28%)	
Drinker	13	(14%)	11	(13%)	

a P-values are from Fisher's exact test for tobacco use and alcohol consumption, from Cochran-Mantel-Haenszel for overall clinical condition, infection status, prior medical evaluation and prior medical treatment, and from ANOVA for number of LRTI infections within past 12 months.

b Tobacco usage comparison was done with respect to two categories: non-user and the combined user and ex-user categories.

c Alcohol consumption comparison was done with respect to two categories: non-drinker and the combined drinker, occasional drinker and ex-drinker categories.

Pretreatment Signs and Symptoms

No statistically significant differences were observed between the treatment groups in pretreatment signs and symptoms in the All-Treated Subjects population. All subjects had cough and were producing sputum at pretreatment. Other frequently reported signs and symptoms at pretreatment for both groups combined included rales/crackling (87%), dyspnea (83%), and rhonchi/wheezing (83%). The table below presents the pretreatment signs and symptoms of All-Treated Subjects.

Summary of Pretreatment Signs and Symptoms (All-Treated Subjects Population)

Sign or Symptom	Number of Subjects by Treatment Group				P-value[a]
	Clarithromycin IR		Trovafloxacin		
Total Treated	95		86		
Cough					0.814
Mild	15	(16%)	10	(12%)	
Moderate	44	(46%)	49	(57%)	
Severe	36	(38%)	27	(31%)	
Sputum Production					0.971
Mild	31	(33%)	29	(34%)	
Moderate	57	(60%)	50	(58%)	
Severe	7	(7%)	7	(8%)	
Sputum Production Volume					0.807
< 1 ounce	45	(47%)	35	(41%)	
1 - 2 ounces	36	(38%)	40	(47%)	
2 - 3 ounces	10	(11%)	9	(10%)	
> 3 ounces	4	(4%)	2	(2%)	
Sputum Appearance					0.180
Mucoid	7	(7%)	15	(17%)	
Mucopurulent	63	(66%)	50	(58%)	
Purulent	25	(26%)	21	(24%)	
Sputum Appearance (Hemoptic)					0.958
Yes	13	(14%)	12	(14%)	
No	82	(86%)	74	(86%)	
Tachypnea					0.504
< 30/min	94	(99%)	84	(98%)	
≥ 30/min	1	(1%)	2	(2%)	
Dyspnea					0.392
Absent	14	(15%)	16	(19%)	
Mild	45	(47%)	40	(47%)	
Moderate	31	(33%)	28	(33%)	
Severe	5	(5%)	2	(2%)	
Rales/Crackling					0.679
Absent	13	(14%)	10	(12%)	
Present	82	(86%)	76	(88%)	
Rhonchi/Wheezing					0.198
Absent	13	(14%)	18	(21%)	
Present	82	(86%)	68	(79%)	

a P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.

Summary of Pretreatment Signs and Symptoms (All-Treated Subjects Population) (Continued)

Sign or Symptom	Number of Subjects by Treatment Group				P-value[a]
	Clarithromycin IR		Trovafloxacin		
Egophony					0.878
Absent	53	(56%)	47	(55%)	
Present	42	(44%)	39	(45%)	
Rigors					0.314
Absent	48	(51%)	37	(43%)	
Present	47	(49%)	49	(57%)	
Pleuritic Pain					0.878
Absent	42	(44%)	39	(45%)	
Present	53	(56%)	47	(55%)	
Fever					0.896
Absent	61	(64%)	55	(64%)	
Present	33	(35%)	31	(36%)	
Not Done@	1	(1%)	0	(0%)	
Oxygenation (Hypoxemia)					0.231
$PO_2 < 60$mmhg	4	(4%)	1	(1%)	
$PO_2 \geq 60$mmhg	44	(46%)	40	(47%)	
Missing@	47	(49%)	45	(52%)	
Peripheral WBC Count					0.657
$< 4500/mm^3$	6	(6%)	5	(6%)	
$4500 - 10000/mm^3$	50	(53%)	49	(57%)	
$>10000/mm^3$	34	(36%)	27	(31%)	
Missing@	5	(5%)	5	(6%)	
Immature Neutrophils (Bands)					0.860
≤ 15%	83	(87%)	75	(87%)	
>15%	5	(5%)	4	(5%)	
Missing@	7	(7%)	7	(8%)	

a P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.
@ Missing values were excluded while calculating the p-values.

Among Clinically Evaluable Subjects, a statistically significant difference was observed between treatment groups in pretreatment sputum appearance (p=0.038); mucopurulent sputum was reported by 65% of the clarithromycin IR group and 55% of the trovafloxacin group, while mucoid sputum was reported by 7% of the clarithromycin IR group and 23% of the trovafloxacin group. No statistically significant differences were observed between the treatment groups in pretreatment signs and symptoms among Clinically and Bacteriologically Evaluable Subjects or Intent-to-Treat Subjects.

Concurrent Medications

Use of medications at pretreatment was similar between the treatment groups for the All-Treated Subjects population; 81% of subjects in the clarithromycin IR group and 79% of the subjects in the trovafloxacin group were taking medications at pretreatment . Overall, the most frequently used therapeutic classifications of medication at pretreatment were analgesics, antipyretics, and anti-inflammatory agents (31%); nonsteroidal anti-inflammatory agents (30%); sympathomimetic agents (26%); expectorants (22%); and antitussives (20%).

At pretreatment and prior to study drug administration, 41% of the subjects in the clarithromycin IR group and 37% of the subjects in the trovafloxacin group were using medications to treat CAP. Overall, the most frequently used acute CAP medications at pretreatment were analgesics, antipyretics, and anti-inflammatory agents (22%); antitussives (20%); expectorants (19%); sympathomimetic agents (14%); and nonsteroidal anti-inflammatory agents (12%).

During the study, 95% of the subjects in the clarithromycin IR group and 97% of the subjects in the trovafloxacin group used concurrent medications. The majority of concurrent medications were used for treatment of coughs, fevers, and other symptoms associated with CAP. Overall, 45% of all subjects used expectorants; 43% used analgesics, antipyretics, and anti-inflammatory agents; 41% used sympathomimetic agents; 40% used opiate agonists; 37% used nonsteroidal anti-inflammatory agents; 22% used antitussives; and 18% used H_1-receptor antagonists. The most frequently used specific medications included [redacted] (42% of subjects), acetaminophen (41%), hydrocodone (28%), albuterol (20%), pseudoephedrine (18%), ibuprofen (17%), acetylsalicylic acid (16%) and dextromethorphan (16%). The percentages of subjects in the clarithromycin IR and trovafloxacin groups who used the above drugs were similar.

Two subjects in the trovafloxacin group were excluded from the bacteriologically and clinically evaluable analyses, because they took medications that could affect the outcome of the study. Four subjects (one clarithromycin IR and three trovafloxacin) 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). The two subjects who were clinically nonevaluable due to confounding medications had no target pathogen isolated pretreatment. Details of the four 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[b]	Indication
Subjects Excluded From Clarithromycin IR Group			
Hosko/1139[a]	prednisone (>10 mg/day)	7 - 17 (10)	Bronchospasm
Subjects Excluded From Trovafloxacin Group			
Honsinger/1016[a] #	Augmentin®	15 (8) - 24 (17)	Otitis media
Jones/1175	prednisone (>10 mg/day)	4 5 6	Asthma

Subject prematurely discontinued from study, bacteriologically and clinically nonevaluable.
a Bacteriologically nonevaluable: no target pathogen isolated pretreatment.
b Number in parentheses indicates days posttreatment.

Pretreatment Susceptibility Results

The target pathogens isolated pretreatment included *H. parainfluenzae* in 35 subjects, *H. influenzae* in 26 subjects, *S. pneumoniae* in 16 subjects, *S. aureus* in 12 subjects, and *M. catarrhalis* in 8 subjects. These target pathogens were tested for *in vitro* susceptibility to the study drugs based on broth dilution MIC and disk diffusion zone size. The susceptibility data for clarithromycin and trovafloxacin are shown in the table below:

Susceptibility of Pretreatment Pathogens to Clarithromycin and Trovafloxacin Based on MIC and Zone Size

		Clarithromycin				Trovafloxacin			
		Based on MIC Results							
Pretreatment Pathogen	Total	S	I	R	No data	S	I	R	No data
Haemophilus parainfluenzae	35	26	9	0	0	35	0	0	0
Haemophilus influenzae	26	21	4	0	1	25	0	0	1
Streptococcus pneumoniae	16	16	0	0	0	16	0	0	0
Staphylococcus aureus	12	11	0	1	0	12	0	0	0
Moraxella catarrhalis	8	8	0	0	0	8	0	0	0
		Based on Zone Size Results							
Haemophilus parainfluenzae	35	22	6	5	2	32	0	0	3
Haemophilus influenzae	26	19	4	1	2	24	0	0	2
Streptococcus pneumoniae	16	16	0	0	0	16	0	0	0
Staphylococcus aureus	12	11	0	1	0	12	0	0	0
Moraxella catarrhalis	8	8	0	0	0	8	0	0	0

S = susceptible; I = intermediate; R = resistant

Based on MIC, only one *S. aureus* isolate was resistant to clarithromycin. The disk and MIC susceptibility data produced generally similar interpretive results. The greatest difference between the methods occurred for *Haemophilus spp.*, where five *H. parainfluenzae* isolates and one *H. influenzae* isolate were resistant to clarithromycin based on disk zone size; none of these isolates were resistant to clarithromycin based on MIC. All of the pathogens isolated were susceptible to trovafloxacin.

Measurement of Treatment Compliance

No statistically significant differences were observed between the treatment groups in duration of treatment and percent compliance in any subject population. In the clinically evaluable population, 99% of the subjects in the clarithromycin IR group and 98% of the subjects in the trovafloxacin group received at least 7 days of treatment and was at least 80% compliant with the treatment regimen. Duration of treatment and study drug compliance for Clinically Evaluable Subjects are presented in the table below:

Duration of Treatment and Study Drug Compliance (Clinically Evaluable Population)

	Clarithromycin IR	Trovafloxacin	P-value[a]
Total Treated	85	66	
Duration of Treatment (Days)			0.532
<3	1 (1%)	0 (0%)	
5 - <7	0 (0%)	1 (2%)	
≥7	84 (99%)	65 (98%)	
Mean (SD)	7.0 (0.59)	7.0 (0.33)	
Minimum - Maximum	2 - 9	5 - 8	
Compliance (percentage)[b]			0.793
20 - <80	1 (1%)	1 (2%)	
≥80	84 (99%)	65 (98%)	
Mean (SD)	99.1 (7.78)	99.4 (3.91)	
Minimum - Maximum	28.6 - 100.0	71.4 - 100.0	

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.

Efficacy Results and Tabulations of Individual Subject Data

Analysis of Efficacy

Clinical response was evaluated in Clinically Evaluable Subjects, Clinically and Bacteriologically Evaluable Subjects, and Intent-to-Treat Subjects. Bacteriological response was evaluated in subjects who were both clinically and bacteriologically evaluable and in Intent-to-Treat Subjects with at least one target pathogen at pretreatment. Radiographic response was evaluated in Clinically Evaluable Subjects, Clinically and Bacteriologically Evaluable Subjects, and Intent-to-Treat Subjects. The Test-of-Cure assessment was made at Evaluation 4 (7 to 28 days posttreatment).

Primary Efficacy Variable

Clinical Cure Rate

Subject Clinical Responses (Clinically Evaluable Subjects)

Among subjects who were clinically evaluable, 89% (76/85) of subjects in the clarithromycin IR group and 95% (63/66) of subjects in the trovafloxacin group were classified as clinical cures at the Test-of-Cure Visit. No statistically significant differences were observed between the treatment groups. 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)

	Clarithromycin IR n/N (%) [95% CI][b]	Trovafloxacin n/N (%) [95% CI][b]	P-value[a] [95% CI][c]
Clinical Cure Rate[d]	76/85 (89%) [80.8, 95.0]	63/66 (95%) [87.3, 99.1]	0.231 [-14.3, 2.2]

a P-value is from Fisher's exact test comparing treatment groups.
b Exact binomial confidence interval.
c Binomial confidence interval for treatment difference based on normal approximation.
d Assessment was made at Evaluation 4 (7-28 days posttreatment) unless the subject was a clinical failure before Evaluation 4. Indeterminates were deleted when calculating the cure rates and p-values.

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

Subject Clinical Responses (Clinically and Bacteriologically Evaluable Subjects)

Among subjects who were both clinically and bacteriologically evaluable, 96% (52/54) of subjects in the clarithromycin IR group and 97% (29/30) of subjects in the trovafloxacin group were classified as clinical cures at the Test-of-Cure Visit. No statistically significant differences were observed between the two treatment groups. 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)			
	Clarithromycin IR n/N (%) [95% CI][b]	Trovafloxacin n/N (%) [95% CI][b]	P-value[a] [95% CI][c]
Clinical Cure Rate[d]	52/54 (96%) [87.3, 99.5]	29/30 (97%) [82.8, 99.9]	>0.999 [-8.5, 7.8]

a P-value is from Fisher's exact test comparing treatment groups.
b Exact binomial confidence interval.
c Binomial confidence interval for treatment difference based on normal approximation.
d Assessment was made at Evaluation 4 (7-28 days posttreatment) unless the subject was a clinical failure before Evaluation 4. Indeterminates were deleted when calculating the cure rates and p-values.

Clinical responses at the Test-of-Cure Visit for bacteriologically and Clinically Evaluable Subjects were also compared using Cochran-Mantel-Haenszel methodology adjusting for potentially influential factors including investigator, sex, race, age, weight, overall clinical condition, infectious status, number of LRTIs within past 12 months, study drug duration, study drug compliance, tobacco use, and alcohol use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Subject Clinical Responses (Intent-to-Treat Subjects)

Among Intent-to-Treat Subjects, 81% (77/95) of the clarithromycin IR group and 76% (65/86) of the trovafloxacin group were classified as clinical cures at the Test-of-Cure Visit. The drop in clinical cure rate from 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. No statistically significant differences were observed between the treatment groups. No statistically significant treatment differences were observed after adjusting for potentially influential factors.

Secondary Efficacy Variables

Subject Clinical Response for Target Pathogens (Clinically and Bacteriologically Evaluable and Intent-to-Treat Subjects)

Among Clinically and Bacteriologically Evaluable Subjects, no statistically significant differences were observed between the treatment groups in clinical cure rates for subjects who had 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)					
	Clarithromycin IR n/N (%)		Trovafloxacin n/N (%)		P-value[a]
Target Pathogen[b]					
H. parainfluenzae	18/19	(95%)	9/9	(100%)	>0.999
H. influenzae	15/15	(100%)	8/9	(89%)	0.375
M. pneumoniae	13/14	(93%)	11/11	(100%)	>0.999
C. pneumoniae	7/9	(78%)	4/4	(100%)	>0.999
S. pneumoniae	7/7	(100%)	3/3	(100%)	not computed
S. aureus	6/6	(100%)	3/3	(100%)	not computed
M. catarrhalis	5/5	(100%)	2/2	(100%)	not computed
L. pneumophila	1/1	(100%)	0/0	-	not computed

a P-values are from Fisher's exact test comparing treatment groups.
b Assessment was made at Evaluation 4 (7-28 days posttreatment) unless the subject was a clinical failure before Evaluation 4. Indeterminates were deleted when calculating the cure rates and p-values.

Subject Bacteriological Cure Rates (Clinically and Bacteriologically Evaluable Subjects)

Among subjects who were both clinically and bacteriologically evaluable, 94% (51/54) of the clarithromycin IR group and 93% (28/30) of the trovafloxacin group were classified as bacteriological cures at the Test-of-Cure Visit. No statistically significant differences were observed between the two treatment groups. 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)			
	Clarithromycin IR n/N (%) [95% CI][b]	Trovafloxacin n/N (%) [95% CI][b]	P-value[a] [95% CI][c]
Bacteriological Cure Rate[d]	51/54 (94%) [84.6, 98.8]	28/30 (93%) [77.9, 99.2]	>0.999 [-9.7, 11.9]

a P-value is from Fisher's exact test comparing treatment groups.
b Exact binomial confidence interval.
c Binomial confidence interval for treatment difference based on normal approximation.
d Assessment was made at Evaluation 4 (7 to 28 days posttreatment) unless the subject was a bacteriological failure before Evaluation 4. Indeterminates were deleted when calculating the cure rates and p-values.

Subject bacteriological responses at the Test-of-Cure Visit for the clinically and bacteriologically evaluable population were also compared using Cochran-Mantel-Haenszel methodology adjusting for potentially influential factors including investigator,

sex, race, age, weight, overall clinical condition, infectious status, number of LRTIs within past 12 months, study drug duration, study drug compliance, tobacco use, and alcohol use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Subject Bacteriological Cure Rates (Intent-to-Treat Subjects)

Among Intent-to-Treat Subjects, 87% (52/60) of the clarithromycin IR group and 71% (30/42) of the trovafloxacin group were classified as bacteriological cures at the Test-of-Cure Visit. 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 analyses.
After adjusting for potentially influential factors, statistically significant differences between eradication rates were observed between the two treatment groups in study drug duration (p=0.049) and study drug compliance (p=0.015).

Pathogen Eradication Rates (Clinically and Bacteriologically Evaluable Subjects)

Among subjects who were both clinically and bacteriologically evaluable, 93% (71/76) of the pathogens identified in the clarithromycin IR group and 95% (39/41) of the pathogens identified in the trovafloxacin group were eradicated after treatment. No statistically significant differences were observed between treatment groups in the overall pathogen eradication rates at the Test-of-Cure Visit.
Among the typical pathogens, all (100%) of the *H. influenzae* (15), *S. pneumoniae* (7), *S. aureus* (6), and *M. catarrhalis* (5) pathogens isolated pretreatment among subjects in the clarithromycin IR group were eradicated after treatment. All (100%) of the *H. parainfluenzae* (9), *S. aureus* (3), and *M. catarrhalis* (2) pathogens isolated pretreatment among subjects in the trovafloxacin group were eradicated after treatment.
Among the atypical pathogens identified pretreatment, all (100%) of the *C. pneumoniae* (4) and *M. pneumoniae* (11) pathogens were eradicated after treatment with trovafloxacin and the only *L. pneumophila* isolate was eradicated after treatment with clarithromycin.
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)

	Clarithromycin IR n/N (%) [95% CI][b]		Trovafloxacin n/N (%) [95% CI][b]		P-value[a] [95% CI][c]
Overall Pathogen Eradication Rate[d]	71/76 [85.3, 97.8]	(93%)	39/41 [83.5, 99.4]	(95%)	>0.999 [-10.3, 6.9]
Eradication Rate[d]					
H. influenzae	15/15	(100%)	8/9	(89%)	0.375
H. parainfluenzae	17/19	(89%)	9/9	(100%)	>0.999
M. pneumoniae	13/14	(93%)	11/11	(100%)	>0.999
C. pneumoniae	7/9	(78%)	4/4	(100%)	>0.999
S. pneumoniae	7/7	(100%)	2/3	(67%)	0.300
S. aureus	6/6	(100%)	3/3	(100%)	not computed
M. catarrhalis	5/5	(100%)	2/2	(100%)	not computed
L. pneumophila	1/1	(100%)	0/0		not computed

a P-value is from Fisher's exact test comparing treatment groups.
b Exact binomial confidence interval.
c Binomial confidence interval for treatment difference based on normal approximation.
d Assessment was made at Evaluation 4 (7-28 days posttreatment) unless the pathogen persisted (i.e., bacteriological failure) before Evaluation 4. Indeterminates were deleted when calculating the cure rates and p-values.

Medical Officer's Comments:

One Investigator (12346 – Patel) enrolled 20 patients in each arm of the study. Out of 40 patients, 11/20 in the clarithromycin arm and 7/20 in the trovofloxacin arm were clinically and bacteriologically evaluable. The numbers of *H. influenzae* isolated in each arm were three. So, even though this investigator contributed to approximately 22% of all patients enrolled in this study, the number of *H. influenzae* isolates were few.

Pathogen Eradication Rates (Intent-to-Treat Subjects)

Among Intent-to-Treat Subjects, the overall pathogen eradication rates at the Test-of-Cure Visit were 85% (72/85) in the clarithromycin IR group and 71% (42/59) in the trovafloxacin group. The eradication rate for *H. influenzae* was 94% (15/16) in the clarithromycin IR group and 80% (8/10) in the trovafloxacin group. The drop in overall pathogen eradication rate from Clinically and Bacteriologically Evaluable Subjects to Intent-to-Treat Subjects is mainly due to the fact that pathogens with indeterminate responses were treated as persistences in the Intent-to-Treat analyses. No statistically significant differences were observed between the treatment groups in the overall eradication rate or in the eradication rate for each of the specific target pathogens. None of the subjects in the clarithromycin IR group developed a superinfection after treatment. One trovafloxacin subject (Investigator Hall, Subject 1076) had a new *H. influenzae* pathogen isolated posttreatment.

Bacteriological Response Versus Clinical Response (Clinically and Bacteriologically Evaluable and Intent-to-Treat Subjects)

Among subjects who were both clinically and bacteriologically evaluable, the subject bacteriologic responses were compared with subject clinical responses in both treatment groups at the Test-of-Cure Visit . Differences occurred in one subject in the clarithromycin IR group and one subject in the trovafloxacin group; both subjects were bacteriological failures and had clinical responses 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 cure and bacteriological eradication.

Radiographic Resolution and Radiographic Success Rates (Clinically Evaluable Subjects)

Among Clinically Evaluable Subjects, 79% (65/82) of the clarithromycin IR group and 82% (54/66) of the trovafloxacin group demonstrated radiographic resolution. Radiographic success (resolution and improvement) rates were 93% (76/82) in the clarithromycin IR group and 95% (63/66) in the trovafloxacin group. No statistically significant differences were observed between the treatment groups in radiographic resolution or radiographic success rates at the Test-of-Cure Visit. A summary of the radiographic resolution and success rates at the Test-of-Cure Visit is presented in the table below for the clinically evaluable subject population.

Radiographic Resolution and Success Rates at the Test-of-Cure Visit (Clinically Evaluable Population)

	Clarithromycin IR n/N (%) [95% CI][a]	Trovafloxacin n/N (%) [95% CI][a]	P-value[b] [95% CI][c]
Radiographic Resolution Rate[d]	65/82 (79%)	54/66 (82%)	0.835
	[68.9, 87.4]	[70.4, 90.2]	[-15.3, 10.2]
Radiographic Success[e] Rate[d]	76/82 (93%)	63/66 (95%)	0.732
	[84.8, 97.3]	[87.3, 99.1]	[-10.3, 4.8]

a Exact binomial confidence interval.
b P-value is from a Fisher's exact test comparing treatment groups.
c Binomial confidence interval for treatment difference based on normal approximation.
d Indeterminate and missing responses were excluded from calculation of radiographic response rates and p-values (clarithromycin IR - 3 subjects).
e Success is defined as subjects who demonstrated resolution or improvement.

Radiographic resolution and success rates at the Test-of-Cure Visit for Clinically Evaluable Subjects were also compared using Cochran-Mantel-Haenszel methodology adjusting for potentially influential factors including investigator, sex, race, age, weight, overall clinical condition, infection status, number of LRTIs within past 12 months, study drug duration, study drug compliance, tobacco use, and alcohol use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Radiographic Resolution and Radiographic Success Rates (Clinically and Bacteriologically Evaluable Subjects)

Among Clinically and Bacteriologically Evaluable Subjects, 85% (44/52) of the clarithromycin IR group and 80% (24/30) of the trovafloxacin group demonstrated radiographic resolution. Radiographic success (resolution and improvement) rates were 96% (50/52) in the clarithromycin IR group and 93% (28/30) in the trovafloxacin group. No statistically significant differences were observed between the treatment groups in radiographic resolution or radiographic success rates at the Test-of-Cure Visit. A summary of the radiographic resolution and success rates at the Test-of-Cure Visit is presented in the table below for the clinically and bacteriologically evaluable subject population.

Radiographic Resolution and Success Rates at the Test-of-Cure Visit (Clinically and Bacteriologically Evaluable Population)

	Clarithromycin IR n/N (%) [95% CI][a]	Trovafloxacin n/N (%) [95% CI][a]	P-value[b] [95% CI][c]
Radiographic Resolution Rate[d]	44/52 (85%) [71.9, 93.1]	24/30 (80%) [61.4, 92.3]	0.762 [-12.7, 22.0]
Radiographic Success[e] Rate[d]	50/52 (96%) [86.8, 99.5]	28/30 (93%) [77.9, 99.2]	0.621 [-7.5, 13.2]

a Exact binomial confidence interval.
b P-value is from a Fisher's exact test comparing treatment groups.
c Binomial confidence interval for treatment difference based on normal approximation.
d Indeterminate and missing responses were excluded from calculation of radiographic response rates and p-values (clarithromycin IR - 2 subjects).
e Success is defined as subjects who demonstrated resolution or improvement.

Radiographic resolution and success rates at the Test-of-Cure Visit for Clinically and Bacteriologically Evaluable Subjects were also compared using Cochran-Mantel-Haenszel methodology adjusting for potentially influential factors including investigator, sex, race, age, weight, overall clinical condition, infection status, number of LRTIs within

past 12 months, study drug duration, study drug compliance, tobacco use, and alcohol use. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Radiographic Resolution and Radiographic Success Rates (Intent-to-Treat Subjects)

Among Intent-to-Treat Subjects, radiographic resolution rates at the Test-of-Cure Visit were 71% (67/95) in the clarithromycin IR group and 65% (56/86) in the trovafloxacin group. Radiographic success (resolution and improvement) rates were 82% (78/95) in the clarithromycin IR group and 76% (65/86) in the trovafloxacin group. No statistically significant differences were observed between the treatment groups in radiographic resolution or radiographic success rates at the Test-of-Cure Visit. No statistically significant treatment differences were observed after adjusting for potentially influential factors.

Resolution/Improvement of Pretreatment Signs and Symptoms at Evaluations 2, 3, and 4

Among Clinically Evaluable Subjects at the During-Therapy Visit (Evaluation 2, Study Days 2-5), statistically significant differences were observed between treatment groups in the percentage of subjects showing resolution in sputum production, sputum production volume, sputum appearance, and rigors, and in the percentage of subjects showing resolution/improvement in sputum appearance. Subjects in the trovafloxacin group demonstrated higher resolution or resolution/improvement rates for these signs/symptoms compared to subjects in the clarithromycin group.

Among Clinically Evaluable Subjects at the Post-Therapy Visit (Evaluation 3, 0 to 6 days posttreatment), there were no statistically significant differences between treatment groups in the percentage of subjects showing resolution or resolution/improvement in any sign or symptom. Additionally, no statistically significant differences were observed between treatment groups for resolution or resolution/improvement of pretreatment signs/symptoms in the clinically and bacteriologically evaluable subject population or the Intent-to-Treat subject population.

Among Clinically Evaluable Subjects at the Test-of-Cure Visit (Evaluation 4, 7 to 28 days posttreatment), there were no statistically significant differences between treatment groups in the percentage of subjects showing resolution or resolution/improvement in any sign or symptom. A summary of the resolution and resolution/improvement rates for all

signs and symptoms at Evaluation 4 is presented in the table below for Clinically Evaluable Subjects.

Resolution and/or Improvement of Pretreatment Signs/Symptoms at the Test-of-Cure Visit (Clinically Evaluable Population)

Sign/Symptom[a]	Clarithromycin IR		Trovafloxacin		P-value[b]
Cough					
Resolution	45/80	(56%)	42/64	(66%)	0.304
Resolution/Improvement	75/80	(94%)	60/64	(94%)	>0.999
Sputum Production					
Resolution	78/80	(98%)	61/64	(95%)	0.656
Resolution/Improvement	80/80	(100%)	63/64	(98%)	0.444
Sputum Production (Volume)					
Resolution	78/80	(98%)	61/64	(95%)	0.656
Resolution/Improvement	79/80	(99%)	63/64	(98%)	>0.999
Sputum Appearance					
Resolution	78/80	(98%)	61/64	(95%)	0.656
Resolution/Improvement	79/80	(99%)	64/64	(100%)	>0.999
Sputum Appearance (Hemoptic)					
Resolution	8/8	(100%)	7/7	(100%)	N/A
Tachypnea					
Resolution	1/1	(100%)	2/2	(100%)	N/A
Dyspnea					
Resolution	61/67	(91%)	45/51	(88%)	0.761
Resolution/Improvement	65/67	(97%)	50/51	(98%)	>0.999
Rales/Crackling					
Resolution	67/67	(100%)	54/56	(96%)	0.205
Rhonchi/Wheezing					
Resolution	63/68	(93%)	46/51	(90%)	0.743
Egophony					
Resolution	35/35	(100%)	29/29	(100%)	N/A
Rigors					
Resolution	38/38	(100%)	33/34	(97%)	0.472
Pleuritic Pain					
Resolution	40/41	(98%)	30/31	(97%)	>0.999
Fever					
Resolution	26/26	(100%)	24/24	(100%)	N/A
Oxygenation (Hypoxemia)					
Resolution	0/1	(0%)	1/1	(100%)	>0.999
Peripheral WBC Count					
Resolution	5/5	(100%)	1/2	(50%)	0.286
Immature Neutrophils (Bands)					
Resolution	2/2	(100%)	0/0	–	N/A

N/A = not applicable

a Pretreatment assessment was made on or before Study Day 1; Evaluation 4 assessment was made between 7-28 days posttreatment.

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

No statistically significant differences were observed between treatment groups for resolution or resolution/improvement of pretreatment signs/symptoms at Evaluation 4 in

the clinically and bacteriologically evaluable subject population or the Intent-to-Treat subject population.

Susceptibility Results

Posttreatment Susceptibility Results

Pretreatment versus posttreatment susceptibilities was evaluated. Based on MIC and zone size results, no isolates became resistant to clarithromycin or trovafloxacin at posttreatment.
No subject had pathogen isolates with an MIC value for clarithromycin or trovafloxacin that increased fourfold or greater from pretreatment to during-treatment or posttreatment. Four subjects had pathogen isolates with decreased zone size values for clarithromycin of 3 mm or more from pretreatment to posttreatment; one of these subjects also had a decreased zone size value for trovafloxacin of 3 mm or more from pretreatment to posttreatment. A summary of the subjects with pathogen isolates showing a ≥3 mm decrease in zone diameter from pretreatment to posttreatment is presented in the table below:

Subjects with Pathogen Isolates Showing a ≥3 mm Decrease in Zone Diameter Pretreatment to Posttreatment

Treatment	Investigator/ Subject #	Study Day	Pathogen	Zone size (mm)	Susceptibility	Clinical Response	Bacteriologic Response
Susceptibility to Clarithromycin							
Clari IR	Stein/1223	1	*H. influenzae*	18	S	Cure	Eradication
		3	*H. influenzae*	14	S		
	Patel/1291	-1	*H. parainfluenzae*	19	S	Cure	Persistence
		20	*H. parainfluenzae*	13	S		
	Patel/1510	1	*H. influenzae*	16	S	Cure	Eradication
		3	*H. influenzae*	11	I		
		9	*H. influenzae*	13	S		
Trova	Hall/1076	1	*S. pneumoniae*	34	S	Cure	Persistence
		22	*S. pneumoniae*	30	S		
Susceptibility to Trovafloxacin							
Trova	Hall/1076	1	*S. pneumoniae*	29	S	Cure	Persistence
		22	*S. pneumoniae*	25	S		

Clari IR = clarithromycin IR; Trova = trovafloxacin; S = susceptible; I = Intermediate

Pretreatment Susceptibility Test Results for Persistent Pathogens

Pretreatment susceptibility results were compared with bacteriological response and clinical response at the Test-of-Cure Visit (Evaluation 4) for the Intent-to-Treat population. A summary of the pretreatment MIC values for each persistent target pathogen and the corresponding subject's clinical response at the Test-of-Cure Visit is presented by treatment group in the table below:

Susceptibility Test Results for Persistent Pathogens								
	Total Number of Pathogens Isolated Pretreatment		Study Drug Assignment					
			Clarithromycin IR			Trovafloxacin		
Pathogen	Clari IR	Trova	Persistent Pathogens	MIC[a]	Clinical Response	Persistent Pathogens	MIC[a]	Clinical Response
H. influenzae	16	10	0			1	≤0.008	failure
S. pneumoniae	9	7	0			1	0.12	cure
						1	0.25	cure
M. catarrhalis	5	3	0			0		
H. parainfluenzae	22	13	1	4	failure	0		
			1	8	cure			
S. aureus	7	5	0			1	0.03	failure

Clari IR = clarithromycin IR; Trova = trovafloxacin; MIC = minimum inhibitory concentration
a MIC at pretreatment

Applicant's Efficacy Conclusions

At the Test-of-Cure Visit, no statistically significant differences were observed between the treatment groups in clinical cure rates, subject bacteriological cure rates, and overall pathogen eradication rates. Similarly, no statistically significant differences were observed in radiographic resolution or success rates. Clinical signs and symptoms of CAP resolved in subjects treated with either regimen.
Results of this study indicate that clarithromycin IR (250 mg BID for 7 days) and trovafloxacin (200 mg QD for 7 days) were equally effective in treating community-acquired pneumonia in adult subjects.

Safety Evaluations

All subjects who received at least one dose of study drug (N=181) were included in the safety analyses (All-Treated Subjects population).

Extent of Exposure

Ninety-five percent (95%) of the 95 subjects assigned to clarithromycin IR and 94% of the 86 subjects assigned to trovafloxacin completed at least 7 days of treatment. 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 IR	Trovafloxacin
Total Treated	95	86
Duration of Treatment (Days)		
<3	3 (3%)	1 (1%)
3 - <5	2 (2%)	2 (2%)
5 -< 7	0 (0%)	2 (2%)
≥7	89 (95%)	80 (94%)
Missing	1	1
Mean (SD)	6.8 (1.17)	6.8 (0.95)
Minimum - Maximum	1 - 9[a]	1 - 8[a]

a Duration of treatment exceeded 7 days for a few subjects who missed doses and did not take study drug consistently for 7 days; no subjects took extra doses of study drug.

Adverse Events

The evaluation of adverse events considered the type, incidence, and severity of events, including and excluding events judged not related or probably not related to the study drugs.

Brief Summary of Adverse Events

The incidence of all treatment-emergent adverse events was 44% of subjects in the clarithromycin IR group and 56% in the trovafloxacin group. Excluding events judged not related or probably not related to study drug, one or more adverse events were reported by 20% of the clarithromycin IR group and 23% of trovafloxacin group. The most common study drug-related adverse events were taste perversion, nausea, and diarrhea in the clarithromycin IR group and nausea, dizziness, vomiting, and constipation in the trovafloxacin group.

Five subjects (four in the clarithromycin IR group and one in the trovafloxacin group) had serious adverse events during the study. All five subjects were hospitalized for treatment of conditions that were considered not related or probably not related to study drug (pneumonia in two subjects, and bronchitis, asthma, and kidney failure in one subject each).

Four subjects (three in the clarithromycin IR group and one in the trovafloxacin group) were prematurely discontinued from treatment due to the occurrence of at least one adverse event. In the clarithromycin IR group, one subject discontinued treatment due to bronchitis that was considered probably not related to study drug administration, one discontinued due to kidney failure that was considered not related, and one discontinued due to gastrointestinal complaints, photosensitivity, taste perversion, and parosmia that were considered probably related. In the trovafloxacin group, one subject discontinued

treatment due to worsening of pneumonia that was considered not related to study drug administration.

Displays of Adverse Events

Of the 181 treated subjects who took study drug, 42 subjects (44%) in the clarithromycin IR group and 48 (56%) in the trovafloxacin group reported at least one treatment-emergent adverse event. The most commonly reported adverse events in the clarithromycin IR group included headache (9%), nausea (7%), taste perversion (6%), and rhinitis (5%). The most commonly reported adverse events in the trovafloxacin group included nausea (8%), headache (7%), dizziness (7%), constipation (6%), insomnia (6%), and vomiting (5%).

Statistically significant differences were observed between treatment groups in the incidence of constipation and insomnia; five (6%) subjects each reported these adverse events in the trovafloxacin group while no subjects in the clarithromycin IR group reported these adverse events.

Most adverse events in both treatment groups were considered mild or moderate in intensity. Eight (8%) subjects in the clarithromycin IR group reported 15 severe events (headache by three subjects, dyspnea by two subjects, and dysphagia, dehydration, arthritis, bone pain, bronchitis, hypoventilation, pharyngitis, pneumonia, rhinitis, and kidney failure by one subject each). Three (3%) subjects in the trovafloxacin group reported four severe events (asthenia, chest pain, joint disorder, and dizziness by one subject each).

A summary of all treatment-emergent adverse events reported by ≥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)

	Clarithromycin IR (N=95) Severity[b]					Trovafloxacin (N=86) Severity[b]				
Adverse Events[a]	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Headache	1	5	3	9	9%	4	2	0	6	7%
Nausea	5	2	0	7	7%	3	4	0	7	8%
Taste perversion	5	1	0	6	6%	1	1	0	2	2%
Rhinitis	2	2	1	5	5%	2	1	0	3	3%
Diarrhea	4	0	0	4	4%	2	0	0	2	2%
Dizziness	3	0	0	3	3%	3	2	1	6	7%
Vomiting	2	1	0	3	3%	2	2	0	4	5%
Pharyngitis	2	0	1	3	3%	2	0	0	2	2%
Infection	1	2	0	3	3%	0	1	0	1	1%
Bronchitis	2	0	1	3	3%	0	0	0	0	0%
Constipation*	0	0	0	0	0%	3	2	0	5	6%
Insomnia*	0	0	0	0	0%	3	2	0	5	6%
Asthenia	0	0	0	0	0%	2	0	1	3	3%

Mod = moderate; Sev = severe

* Statistically significant ($p \leq 0.05$) difference between treatment groups.

a Adverse events occurring in ≥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, 20% (19/95) of subjects in the clarithromycin IR group and 23% (20/86) of subjects in the trovafloxacin group reported at least one adverse event considered possibly or probably related to study drug therapy. The most commonly reported treatment-related adverse events in the clarithromycin IR group included taste perversion (6%), nausea (4%), and diarrhea (3%). The most commonly reported adverse events in the trovafloxacin group included nausea (5%), dizziness (5%), vomiting (3%), and constipation (3%).

A summary of adverse events, excluding events judged not related or probably not related to study drugs, reported by ≥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 (Excluding Events Judged Not Related or Probably Not Related to Study Drugs)

	Clarithromycin IR (N=95) Severity[b]					Trovafloxacin (N=86) Severity[b]				
Adverse Events[a]	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Taste perversion	5	1	0	6	6%	1	1	0	2	2%
Nausea	3	1	0	4	4%	1	3	0	4	5%
Diarrhea	3	0	0	3	3%	1	0	0	1	1%
Dizziness	2	0	0	2	2%	1	2	1	4	5%
Vomiting	0	1	0	1	1%	1	2	0	3	3%
Constipation	0	0	0	0	0%	2	1	0	3	3%

Mod = moderate; Sev = severe

a Adverse events occurring in ≥3% of subjects in either treatment group.

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

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

No deaths were reported that occurred during treatment or within 30 days after the last dose of study drug.

Other Serious Adverse Events

Five subjects (four in the clarithromycin IR group and one in the trovafloxacin group) experienced serious adverse events. All but one (kidney failure, Patel 1069, clarithromycin IR group) of these adverse events were associated with the respiratory system. All of the serious adverse events were considered by the investigator to be not related or probably not related to study drug administration.

Other Significant Adverse Events

Four subjects (three in the clarithromycin IR group and one in the trovafloxacin group) experienced adverse events that resulted in premature discontinuation of study drug. In the clarithromycin IR group, one subject discontinued treatment due to bronchitis that was considered probably not related to study drug administration, one discontinued due to kidney failure that was considered not related, and one discontinued due to

gastrointestinal complaints, photosensitivity, taste perversion, and parosmia considered probably related. In the trovafloxacin group, one subject discontinued treatment due to worsening of pneumonia that was considered not related to study drug administration.

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

Five subjects (four in the clarithromycin IR group and one in the trovafloxacin group) had serious adverse events during the study. Serious adverse events included worsening pneumonia for two subjects, and asthma, kidney failure, and bronchitis for one subject each; all of these events were considered serious, because they resulted in hospitalization. Each of the serious adverse events was considered not related or probably not related to study drug. Details concerning subjects who had serious adverse events are displayed by treatment group in the table below:

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 IR Treatment Group with Serious Adverse Events						
Honsinger/1017	55/F	1	10 (3)	Respiratory	Asthma	Hospitalization
Patel/1069#	75/M	1	13 (12)	Urogenital	Kidney failure	Hospitalization
Nadeemullah/1254#	49/M	4 (1)	6 (3)	Respiratory	Bronchitis	Hospitalization
Sheikh/1560	59/F	9 (2)	12 (5)	Respiratory	Pneumonia	Hospitalization
Subjects in the Trovafloxacin Treatment Group with Serious Adverse Events						
Degarmo/1087#	61/F	6 (1)	11 (6)	Respiratory	Pneumonia	Hospitalization

\# Subject prematurely discontinued the study.
a Numbers in parentheses are days relative to last dose of study drug.

Three subjects in the clarithromycin IR group and one subject in the trovafloxacin group were prematurely discontinued from treatment due to the occurrence of at least one adverse event. Details concerning subjects who discontinued study drug 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[a]	Day of Resolution[a]	Body System	COSTART Term
Subjects Discontinued from the Clarithromycin IR Treatment Group					
Patel/1069	75/M	1	13 (12)	Urogenital	Kidney failure
Jones/1027	37/F	2	7 (5)	Digestive	GI disorder[b]
		2	3 (1)	Digestive	Nausea[b]
		2	6 (4)	Body as a Whole	Photosensitivity Rx[b]
		2	6 (4)	Special Senses	Parosmia[b]
		2	4 (2)	Special Senses	Taste perversion[b]
		2	3 (1)	Digestive System	Vomiting[b]
Nadeemullah/1254	49/M	4 (1)	6 (3)	Respiratory	Bronchitis
Subjects Discontinued from the Trovafloxacin Treatment Group					
Degarmo/1087	61/F	6 (1)	11 (6)	Respiratory	Pneumonia

GI = gastrointestinal; Rx = reaction
A Numbers in parentheses are days relative to last dose of study drug.
B Drug-relationship classified as probable.

Clinical Laboratory Evaluation

Laboratory Value

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. No obvious differences were observed between the treatment groups.

Individual Clinically Significant Abnormalities

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

Subjects with Serum Chemistry Values That Met Sponsor-Defined Possibly Clinically Significant Criteria							
Investigator/ Subject Number	Age (yrs)/ Sex	Variable	Baseline Value[a]	Study Day[b]	Possibly Significant Value	Final Value	CS Criteria
Subjects in the Clarithromycin IR Treatment Group							
Hall/1073	30/M	ALT/SGPT (U/L)	21	9 (2)	165 H	165 H	3xULN
Subjects in the Trovafloxacin Treatment Group							
Tarshis/1102	59/F	BUN (mg/dL)	17	8 (1)	30 H	30 H	1.25xULN

Reference ranges: BUN = 4 - 24 mg/dL; ALT/SGPT = 6-43 (males).
H = above normal reference range;
CS = Clinically significant; ULN = Upper limit of normal;
a Baseline is last value before study drug administration.
b Numbers in parentheses are days relative to last dose of study drug.

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.
One subject in the clarithromycin IR group and three subjects in the trovafloxacin group had values for vital signs that met sponsor-defined possibly clinically significant criteria. Three subjects (one clarithromycin IR and two trovafloxacin) 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 remaining subject had a change in pulse rate. Investigator Acampora, Subject 1312 in the trovafloxacin group had a baseline pulse of 90 bpm that increased to 120 bpm on Study Day 3. This subject's subsequent pulse was recorded as 80 bpm and 92 bpm on Study Days 9 and 23, respectively. The high pulse on Day 3 was considered by the investigator to be of no clinical concern.

Safety Conclusions

No statistically significant differences were observed between the clarithromycin IR and trovafloxacin groups in the overall incidence of treatment-related adverse events (20% and 23%, respectively). The most common treatment-related adverse events were taste perversion (6%), nausea (4%), and diarrhea (3%) in the clarithromycin IR group and nausea (5%), dizziness (5%), vomiting (3%), and constipation (3%) in the trovafloxacin group.
Five subjects (4 in the clarithromycin IR group and 1 in the trovafloxacin group) had serious adverse events during the study; all 5 subjects were hospitalized for treatment of conditions that were considered not related or probably not related to study drug. Four subjects (3 in the clarithromycin IR group and 1 in the trovafloxacin group) were

prematurely discontinued from treatment due to the occurrence of adverse events. Adverse events for one of these subjects were considered possibly related to study drug. Changes in laboratory and vital signs were minor and were not considered clinically significant. Both clarithromycin IR and trovafloxacin were safe and well-tolerated.

Applicant's Overall Conclusions

Clarithromycin IR tablets are indicated for the treatment of pneumonia due to *M. pneumoniae*, *S. pneumoniae*, or *C. pneumoniae*. Trovafloxacin tablets are indicated for the treatment of pneumonia caused by *S. pneumoniae*, *H. influenzae*, *K. pneumoniae*, *S. aureus*, *M. pneumoniae*, *M. catarrhalis*, *L. pneumophila*, or *C. pneumoniae*.
In this study, clarithromycin IR and trovafloxacin were compared for clinical, bacteriological, and radiological efficacy in the treatment of community-acquired pneumonia. As expected, there were no statistically significant differences in clinical response, subject bacteriological response, overall pathogen eradication, and radiological response. At the Test-of-Cure Visit (Evaluation 4) in Clinically Evaluable Subjects, clinical cure rates were 89% in the clarithromycin IR group and 95% in the trovafloxacin group. Similarly, in Clinically and Bacteriologically Evaluable Subjects, bacteriological cure rates were 94% in the clarithromycin IR group and 93% in the trovafloxacin group. Overall pathogen eradication rates were 93% in the clarithromycin IR group and 95% in the trovafloxacin group. Radiographic success (resolution and improvement) rates among Clinically Evaluable Subjects were 93% and 95% in the clarithromycin IR and trovafloxacin groups, respectively. Clinical signs and symptoms of CAP resolved in subjects treated with either regimen, with no statistically significant differences between the treatment groups at the Test-of-Cure Visit.
The efficacy of clarithromycin IR and trovafloxacin in the eradication of eight target pathogens was examined: *H. influenzae*, *H. parainfluenzae*, *S. aureus*, *M. pneumoniae*, *L. pneumophila*, *C. pneumoniae*, *S. pneumoniae*, and *M. catarrhalis*. Three of the pathogens, *M. pneumoniae*, *S. pneumoniae*, and *C. pneumoniae*, are included in the current label for clarithromycin IR, while all of them except *H. parainfluenzae*, as well as *K. pneumoniae*, are included in the product label for trovafloxacin. The eradication rates for the target pathogens were similar in the two treatment groups. Of note, the eradication rate for *H. influenzae* in the clarithromycin IR was 100% (15/15). This eradication rate was similar to that of trovafloxacin (8/9, 89%) which was approved for the treatment of pneumonia caused by *H. influenzae*.
Excluding adverse events judged not related or probably not related to study drugs, the incidence of adverse events was similar in the treatment groups (20% clarithromycin IR; 23% trovafloxacin). Most adverse events in both treatment groups were considered mild or moderate in intensity. Five subjects had serious adverse events during the study, all of which were hospitalizations for treatment of conditions not related or probably not related to study drug administration. Four subjects discontinued treatment due to adverse events; only one subject discontinued study drug due to treatment-related adverse events. No deaths were reported in this study.
Results of this study indicated that clarithromycin IR (250 mg BID for 7 days) was comparable to trovafloxacin (200 mg QD for 7 days) in treating adults with community-acquired pneumonia. Both treatment regimens were effective in eradicating the target pathogens, resolving clinical signs and symptoms of pneumonia, and resolving or

improving radiographic evidence of pneumonia. Clarithromycin IR and trovafloxacin were both safe and well-tolerated.

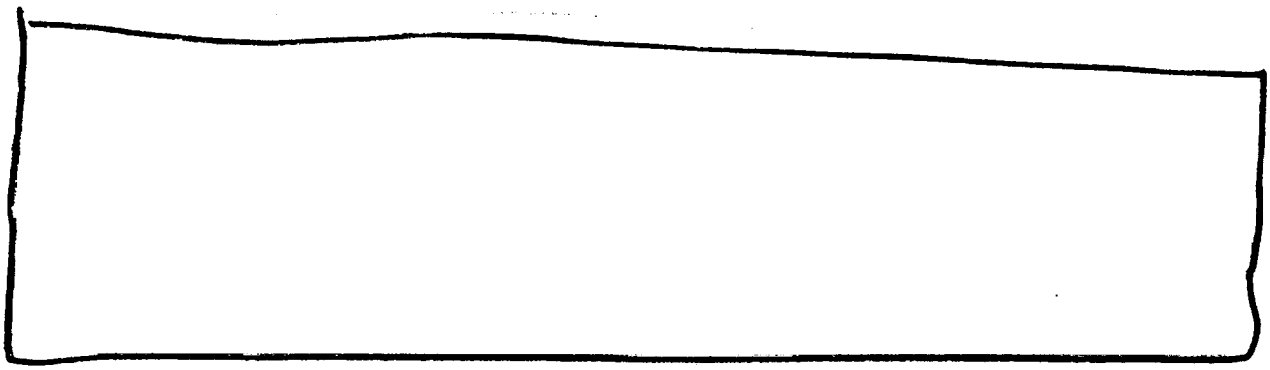
Medical Officer's Overall Conclusions

The applicant submitted data from one clinical study in support of adding the microorganism *H. influenzae* to the Community-Acquired Pneumonia indication. In this study, clarithromycin IR and trovafloxacin were compared for clinical, bacteriological, and radiological efficacy in the treatment of community-acquired pneumonia. The clinical cure rates at the Test-of-Cure Visit (Evaluation 4) in Clinically Evaluable Subjects, were 89% in the clarithromycin IR group and 95% in the trovafloxacin group. Similarly, in Clinically and Bacteriologically Evaluable Subjects, bacteriological cure rates were 94% in the clarithromycin IR group and 93% in the trovafloxacin group. Overall pathogen eradication rates were 93% in the clarithromycin IR group and 95% in the trovafloxacin group. Radiographic success (resolution and improvement) rates among Clinically Evaluable Subjects were 93% and 95% in the clarithromycin IR and trovafloxacin groups, respectively.
The eradication rate for *H. influenzae* in the clarithromycin IR was 100% (15/15). This eradication rate was similar to that of trovafloxacin (8/9, 89%) which was approved for the treatment of pneumonia caused by *H. influenzae*.
Ninety-five percent (95%) of the 95 subjects assigned to clarithromycin IR and 94% of the 86 subjects assigned to trovafloxacin completed at least 7 days of treatment.

The incidence of adverse events was similar in the treatment groups, 20% in the clarithromycin IR group and 23% in the trovafloxacin group. Most adverse events in both treatment groups were considered mild or moderate in intensity. Five subjects had serious adverse events during the study, all of which were hospitalizations for treatment of conditions not related or probably not related to study drug administration. Four subjects discontinued treatment due to adverse events; only one subject discontinued study drug due to treatment-related adverse events. No deaths were reported in this study.
The applicant has requested the following addition (written in bold) to the INDICATIONS AND USAGE section of the package insert:

Medical Officer's Recommendations

This supplement is recommended for approval based upon the data submitted by the applicant. The package insert for Biaxin Filmtabs should incorporate the following changes to the INDICATIONS AND USAGE and the DOSAGE AND ADMINISTRATION sections:



The above recommendations should be conveyed to the applicant of this NDA supplement.

/S/

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

CC: Original NDA 50-662/S-029
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/NMoledina
HFD-520/Pharm/ROsterberg
HFD-520/Micro/SAltaie
HFD-520/Chem/AYu
HFD-725/Biostat/JJiang
HFD-420/BioPharm/FPelsor
HFD-520/PM/JCintron
nm/04-24-2000/rev 05-24-2000.

Concurrence Only:
HFD-520/DivDir/GChikami /S/ 7/20/2000
HFD-520/MTL/MSAlbuerne
Rec'd 4/28/00 (draft)
5/25/00 (final)