cases were small and do not provide a strong evidence of efficacy. In the bacteriological MITT population, the eradication rate was only 5/10 (50%).

Table 22: All CAP Studies: Clinical and Bacteriological Responses (Pen-Resistant)	
	n/N
Bacteriological PP	**16/19**
Pen-Resistant Only	8/8
Blood	3/3
Sputum	5/5
Pen and Erythromycin Resistant	8/11
Blood	2/4
Sputum	6/7
Bacteriological MITT	**19/28**
Pen-Resistant Only	9/12
Blood	3/5
Sputum	6/7
Pen and Erythromycin Resistant	10/16
Blood	2/5
Sputum	8/11

Statistical Reviewer's Comments:

CAP patients with bactermia due to PRSP, the clinical and bacteriological cure rates were 5/7(71.4%) in the PP population and 5/10 (50%) in the MITT population. The numbers of isolates were too small to meaningfully conclude efficacy.

Table 23: All CAP Studies: Bacteriological Responses (Pen-Resistant patients) Based on blood and Sputum			
	n/N	(%)	95% CI
Bacteriological PP (n=19)			
Blood	5/7	(71.4%)	(29.0, 96.3)
Fine scores			
I	3/3		
II	2/3		
III	0/1		
Sputum	11/12	(91.7%)	(61.5, 99.8)
Fine scores			
I	7/7		
II	2/2		
III	2/2		
IV	0/1		
Bacteriological MITT(n=28)			
Blood	6/10	(60.0%)	(26.2, 87.8)
Fine scores			
I	3/4		
II	2/3		
III	1/3		
Sputum			
Fine scores	15/18	(83.3%)	(58.6, 96.4)
I	8/8		
II	4/5		
III	3/3		
IV	0/1		
V	0/1		

Statistical Reviewer's Comments:

In the PPb population with PRSP isolates, the fine scores among the 7 bacteremic cases yielded only one case with a fine score of III which was a failure and in the MITT population, eradication rate among the cases with fine score of III was 1/3.

Table 24: Relationship Between Telithromycin MIC and Penicillin MIC (PP)			
		Penicillin MIC of PRSP Isolate	
		2.0 ug/ml	8.0 ug/ml
Tel MIC	0.008	2	1
	0.015	2	0
	0.03	6	0
	0.06	2	0
	0.12	2	0
	0.25	1	0
	0.5	2	0
	1.0	1	0
	Total	**18**	**1**

Statistical Reviewer's Comments:

Among Penicillin MIC=2.0 ug/ml, all the isolates had a telithromycin MIC ranging from 0.008-1.0. Only one isolate had a PCN MIC of 8.0 ug/ml. Among the isolates, 18/19 (95%) had a penicillin MIC of 2ug/ml. Overall, there was enough disparity between the PCN MIC and the Tel MIC that it can be concluded that no consistent prediction can be made on the Tel MIC based on the PCN MIC.

Table 25: All CAP Studies: Clinical and Bacteriological Responses (Erythromycin Resistant patients)			
	n/N	(%)	95% CI[a]
Bacteriological PP	25/29	(86.2)	(68.3, 96.1)
Erythromycin only	17/18		
Blood	6/6		
Sputum	11/12		
Pen and Erythromycin	8/11		
Blood	2/4		
Sputum	6/7		
Bacteriological MITT	29/37	(78.3)	(61.8, 90.2)
Erythromycin only	19/21		
Blood	6/6		
Sputum	13/15		
Pen and Erythromycin	10/16		
Blood	2/5		
Sputum	8/11		

Statistical Reviewer's Comments:

In the PPb population, among the macrolide- (erythromycin A-) resistant S. pneumoniae (ERSP) isolates, the bacteriological eradication rate was 25/29 (86.2%; 95% CI: 68.3, 96.1). Of which, 17/18 isolates were Erythromycin only and 8/11 with both Penicillin and Erythromycin resistant isolates. In the MITT population, the bacteriological eradication rate for ERSP was 29/37 (78.3%; 95% CI: 61.8., 90.2). Among the bacteremia patients with ERSP, the clinical cure rate was 8/10 in the PP population and 8/11 in the MITT population.

Table 26: Relationship Between Telithromycin MIC and Erythromycin MIC (PP)

		Erythromycin MIC of ERSP Isolate (n=29)							
		2	4	8	16	32	128	256	512
Tel MIC	0.016	0	0	0	0	0	0	1◆	0
	0.03	0	1♣	0	0	3◆	1*	2◆	2◆
	0.06	1♣	2♣	1♣	0	0	0	1◆	0
	0.12	0	1♣	4◆♣	0	0	0	0	0
	0.25	0	0	0	0	0	0	0	1◆
	0.5	0	0	0	0	0	0	1*	2#
	1	0	0	2◆♣	2♣	1♣	0	0	0
	Total	**1**	**4**	**7**	**2**	**4**	**1**	**5**	**5**

* ermA , ◆ ermB, # ermB/mef E, ♣ mefE

Statistical Reviewer's Comments:

Among ERSP isolates, there is no specific pattern or trend observed and there is enough disparity between the ERSP MIC and the Tel MIC that it can be concluded that no consistent prediction can be made on the Tel MIC based on the ERSP MICs. Also, from the above table it is evident that for mefE genotypes, most of the isolates are clustered at low ERSP MICs and for ermB, the isolates were clustered at higher ERSP MICs, probably showing an association between the genotypes (mefE and ErmB) and the ERSP MICs.

Table 27: All CAP Studies: Genotypes (Erythromycin Resistant patients-**PP**)

Genotypes	Number of Patients (%)	Clinical · Bacteriological Response*	Erythromycin Resistant only	Penicillin and Erythromycin **Resistant**
ermB	11 (38%)	9/11 (81.8%)	7/7	2/4
ermA/ermB	2 (7%)	2/2	2/2	0/0
mefE	13 (45%)	11/13 (84.6%)	7/8	4/5
ermB/mefE	2 (7%)	2/2	0/0	2/2
Missing Value	1 (3%)	1/1	1/1	0/0

* Clinical Cure and Bacteriological Responses

Statistical Reviewer's Comments:

Among the 29 isolates in the PPb population most of the isolates were either genotypes ermB (38%) and mefE(45%) and the eradication rates were 9/11 (81.8%) and 11/13 (84.6%) respectively. Among the isolates, 18 (62%) were Erythromycin-only resistant and 11 for both PRSP and ERSP. In the latter group of multiple resistance, the isolates with an ermB genotype, an eradication rate of 2/4(50%) was observed compared to other genotypes.

Results based on Japanese Trials:

Based on the Japanese studies (trials 2105 and 3107), subjects with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A from single or mixed pathogen infections were analysed.

Table 28: Japanese Trials: PP-Population

	n/N			
	Trial 2105		Trial 3107	
	Bacteriological Response	Clinical Response	Bacteriological Response	Clinical Response
Penicillin Resistant only	0/0	0/0	0/0	0/0
Erythromycin Resistance only	6/6	5/6	5/7	6/7
Penicillin and Erythromycin only	3/3	3/3	5/5	5/5

Statistical Reviewer's Comments:

In the PP population(including both trials), there were 8 isolates with Penicillin G-resistant S. pneumoniae and all of them were clinical and bacteriological cures. Among the 21 macrolide- (erythromycin A-) resistant S. pneumoniae, 19/21(90.5%, 95% CI: 69.6, 98.8) were clinical and bacteriological cures. There were no bacteremic patients.

Table 29: Japanese Studies: Genotypes (Erythromycin Resistant patients-**PP**)

Genotypes	Number of Patients (%)	Clinical / Bacteriological Response

ermB	15 (71.4%)	13/15
ermB/mefE	1(4.8%)	1/1
mefA	5 (23.8%)	5/5

Statistical Reviewer's Comments:

Among the 21 isolates in the PPb population most of the isolates belong to either genotypes ermB (71%) and mefA(24%) and the eradication rates were 13/15 and 5/5 respectively.

Conclusions and Recommendations

In the PP population, there were 19 isolates with Penicillin G-resistant S. pneumoniae, of which 16/19 (84.2%, 95% CI: 60.4, 96.6) were clinical cures and in the MITT population, there were 28 isolates with Penicillin G-resistant S. pneumoniae, of which 19/28 (67.9%, 95% CI: 47.6, 84.1) were clinical cures. Similar bacteriological cure rates were observed in the PP population. The cure rates in the MITT population was considerably low compared to PP population. Based on the sponsor's results, of the 9 additional patients in the MITT, 4 of them had an fine score of 3 or greater. The numbers of isolates were too small to make any statistically meaningful conclusion.

In the PP population, among the 29 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, of which 25/29 (86.2%, 95% CI: 68.3, 96.1) were clinical cures and in the MITT population, of the 37 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, 29/37 (78.4%, 95% CI:61.8, 90.2) were clinical cures.

The cure rates among the subjects with both PRSP and ERSP isolates were; 8/11 (73%) in the PP and 10/16 (62.5%) in the MITT populations.

Among the bacteremic patients due to PRSP, the clinical cure rate was 5/7 (71.4%) in the PP population and 5/10 (50%) in the MITT population. For bacteremia due to ERSP, the clinical cure rate was 8/10 in the PP and 8/11 in the MITT populations.

Assessing based on the genotypes, among the 29 ERSP isolates in the PPb population, most of the isolates were either genotypes ermB (38%) and mefE(45%). The eradication rates for both genotypes were 9/11 (81.8%) and 11/13 (84.6%) respectively. Of the total number of ERSP cases, 18 (62%) were Erythromycin-only resistant and 11 for both PRSP and ERSP. In the latter group of multiple resistance, the isolates with an ermB genotype, an eradication rate of 2/4(50%) was observed compared to other genotypes.

Based on the Japanese studies, subjects with S. pneumoniae isolates resistant to penicillin G and/or erythromycin A, in the PP population among those with PRSP and ERSP, there were 8/8 clinical and bacteriological cures. Among the 21 macrolide- (erythromycin A-) resistant S. pneumoniae, 19/21(90.5%, 95%CI: 69.6, 98.8) were clinical and bacteriological cures. There were no bacteremic patients in the group.

Overall, based on the data, there were no substantial evidence available in support of the efficacy of this drug in the treatment of CAP due to PRSP or ERSP isolates. There are limited numbers of bacteremic patients with relatively low success rates.

2.3.2.2 Acute Bacterial Sinusitis

Subjects with S. Pneumoniae Resistance

Table 30: All ABS Studies: All Resistant Cases MITT (n=29)	
Penicillin Resistant	3
Erythromycin Resistant	13
Penicillin and Erythromycin Resistant	13

Statistical Reviewer's Comments:

Based on FDA analysis, in the MITT population with the single or mixed pathogen infections, there were a total of 29 isolates with Penicillin G-resistant S. pneumoniae (PRSP) and macrolide- (erythromycin A-) resistant S. pneumoniae (ERSP). There were 16 Penicillin G-resistant and 26 macrolide- (erythromycin A-) resistant S. pneumoniae isolates in the MITT population.

Table 31: All ABS Studies: Bacteriological Responses (PP)	
	n/N
Penicillin Resistant only	2/2
Erythromycin Resistance only	9/10
Penicillin and Erythromycin only	9/11

Statistical Reviewer's Comments:

In the bacteriological PP population among the single or mixed pathogen infections, there were 13 isolates with Penicillin G-resistant S. pneumoniae, of which 11/13 (84.6%, 95% CI:54.6,98.1) were clinical and microbiological cures and 21 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, of which 18/21 (85.7%, 95%CI: 63.7, 97.0), were clinical and microbiological cures. The cure rates among the subjects with both PRSP and ERSP isolates was 9/11(73%).

Table 32: All ABS Studies: Bacteriological Responses (MITT)	
	n/N
Penicillin Resistant only	3/3
Erythromycin Resistance only	10/13
Penicillin and Erythromycin only	11/13

Statistical Reviewer's Comments:

In the MITT population, there were 16 isolates with Penicillin G-resistant S. pneumoniae, of which 14/16 (87.5%, 95% CI:61.7, 98.4) were clinical and bacteriological cures and 26 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, of which 21/26 (80.8%, 95% CI:60.6, 93.4) were clinical and bacteriological cures. The cure rates among the subjects with both PRSP and ERSP isolates were 11/13 (85%).

Table 33: All ABS Studies: PRSP Outcomes (PPb)		
Study	Treatment	n/N Clinical Cure
3002	5-days 10-days	1/1 2/2
3005	10-days	1/1
3011	5-days	7/9

Statistical Reviewer's Comments:

The applicant has requested for 5-day treatment of sinusitis with telithromycin. Based on studies 3002 and 3011, there were only 10 patients with PRSP and the clinical cure rate is 8/10 (80%). The numbers are too small to make any statistically valid conclusion.

Table 34: Genotypes among Erythromycin Resistant cases **(PPb)**		
Genotypes	Number of Patients (%)	Clinical / Bacteriological Response
ermB	12/21 (57.1%)	12/12 (100%)
mefE	9/21 (42.8%)	6/9 (66.7%)

(bMITT)		
ermB	15/26 (57.7%)	14/15 (93.3%)
mefE	11/26 (42.3%)	7/11 (63.6%)

Statistical Reviewer's Comments:

Among the 21 isolates in the PPb population with macrolide resistant isolates, ermB genotypes were among 57.1% with a cure rate of 12/12(100%) and 42.8% of the remaining were with mefE genptypes and had an eradication rate of 6/9 (66.7%). In the bMITT population, the distribution of ermB and mefE were similar as in the PP population, but the ermB genotype had a cure rate of 14/15(93%) compared to mefE with a rate of 7/11(63.3%). The numbers of isolates were not large enough among the genotypes and a strong association cannot be drawn based on the results.

Conclusions and Recommendations

In the bacteriological PP population, there were 13 isolates with Penicillin G-resistant S. pneumoniae, of which 11/13 (84.6%, 95% CI:54.6,98.1) were clinical and bacteriological cures and in the MITT population, there were 16 isolates with Penicillin G-resistant S. pneumoniae, of which 14/16 (87.5%, 95% CI:61.7, 98.4) were clinical and bacteriological cures. The cure rates among the subjects with both PRSP and ERSP isolates in the PP and MITT were 9/11(73%) and 11/13 (85%) respectively.

Among the 21 isolates in the PP population with macrolide- (erythromycin A-) resistant S. pneumoniae, 18/21 (85.7%, 95%CI: 63.7, 97.0), were clinical and microbiological cures. Among the 26 isolates in the MITT population, 21/26 (80.8%, 95% CI:60.6, 93.4) were cures.

Overall, based on the data submitted, there is not enough evidence to support the claim for PRSP or ERSP. Since the applicant has requested for 5-day treatment of sinusitis with telithromycin, there were only 10 patients with PRSP and 14 patients with ERSP. In the PP population, the clinical cure rate was 8/10 (80%) for PRSP and 12/14 (86%) for ERSP. The evidence is substantially low due to smaller number of isolates and it is difficult to draw any statistically meaningful conclusion.

2.3.3 Acute Exacerbation of Chronic Bronchitis (AECB)

2.3.3.1 Study 3013

Design and Objectives

This was a multicenter, double-blinded, active-controlled, comparative, randomized, two-armed, parallel-group (1:1) study. Subjects were enrolled at a total of 105 study sites in the following countries: Argentina (7 sites), Australia/New Zealand (7 sites), Belgium (2 sites), Brazil (4 sites), Canada (6 sites), Chile (3 sites), Germany (7 sites), Italy (4 sites), Mexico (3 sites), South Africa (6 sites), Spain (2 sites), Turkey (5 sites), and the United States (49 sites).

Based on the sponsor's submission, at the pretherapy/entry visit (day 1), subjects were randomized in a double-blinded fashion to study treatment upon qualifying for entry into the study. An on-therapy visit was to be performed at days 3 to 5. Subjects were to complete further visits at end of therapy (days 11 to 13), posttherapy/test of cure (TOC) (days 17 to 21), late posttherapy (days 31 to 36), and the time to next exacerbation up to 6 months.

Primary objective:

The primary objective of this study was to demonstrate equivalence in clinical efficacy and assess safety of oral telithromycin 800 mg once daily given for 5 days versus oral clarithromycin 500 mg given twice daily for 10 days as treatment for Acute Exacerbation of Chronic Bronchitis (AECB) due to common bacterial as well as atypical and intracellular pathogens in adult subjects. The primary efficacy endpoint was clinical outcome at post-therapy/TOC.

Secondary objectives:

The secondary objective of this study was to compare bacteriological efficacy of oral telithromycin 800 mg once daily given for 5 days and oral clarithromycin 500 mg given twice daily for 10 days as treatment for AECB for documented cases in adults.

Statistical Reviewer's Comments:

Testing the equivalence of treatment differences with respect to the efficacy variables were assessed based on a two-tailed 95% confidence interval of the difference in clinical and microbiological cure rates. The primary efficacy analysis would be evaluated using a non-inferiority margin (delta) of 10% (based on the MO's assessment). The robustness of the primary efficacy results will be assessed using the Evaluable and the ITT and/or the MITT populations.

The primary efficacy variable for this study was the clinical outcome at the posttherapy/TOC visit was evaluated by the investigator according to the following definitions:

Cure (Sponsor classified based on any of the following)::

1. Return to preinfection state: AECB infection-related signs and symptoms had disappeared or had returned to the preinfection state.

2. Postinfectious stigmata: remaining AECB infection-related signs and symptoms representing a normal clearance of infection and no subsequent antibiotic therapy was started for treatment of the disease under investigation.

Failure(Sponsor classified based on any of the following):

1. Unchanged: all AECB infection-related signs and symptoms had remained unchanged.
2. Worsened: AECB related signs and symptoms had worsened.
3. Not improved sufficiently and new antibiotics or subsequent treatment added: one or more antibiotics or subsequent treatment was added to the study treatment for the disease under investigation due to insufficient clinical improvement.
4. New clinical findings: The subject developed new clinical findings consistent with active infection.
5. The subject died due to the infectious disease.
6. New antibiotic required in the following specific, indirect, situations associated with insufficient improvement: adverse event(s) that led to discontinuation, non-compliance, or bacterial persistence.

Demographics and Baseline Characteristics

Table 35: Number of subjects in each analysis population

Population	TEL 5-day	CLA 10-day
Total treated	272	282
mITT	270	282
PPc	225	231
bmITT	90	88
PPb	72	76

Sponsor's Table
PPc=All mITT subjects excluding those with major protocol violations
PPb=All PPc subjects with bacteriologically proven infection
bmITT=All mITT subjects containing at least one pathogen responsible for infection

Table 36: Reasons for exclusion from mITT and PPb, and summary of major protocol violations for PPc

Reasons for exclusion and major protocol violations	Number of subjects TEL 5-day	CLA 10-day
Total treated (ITT)	272	282
Total excluded from mITT analysis	2	0
Subjects with chest x-ray at pretherapy/entry confirming pneumonia	2	0
Total included in mITT analysis	270	282
Total excluded from PPc analysis	45	51
Reasons for exclusion from PPc analysis:		
Insufficient treatment duration	17	18
Age less than 30 years old	8	9
Insufficient signs at pretherapy/entry	5	9
Missing appropriate posttreatment information (except failure)	9	4
Inability to determine clinical outcome at posttherapy/TOC	4	8
Sputum collection not witnessed	3	5
Treatment discontinued a posteriori due to laboratory exclusion criteria at entry	3	1
Previous antimicrobial treatment	1	0
Use of nonstudy systemic antimicrobial between pretherapy/entry and posttherapy/TOC	0	2
Inability to collect sputum at visit 1	0	2
Total included in PPc analysis	225	231
Total excluded from PPb analysis:	153	155
Reasons for exclusion from PPb analysis:		
Without valid causative pathogen at pretherapy/entry	117	118
Without adequate culture at pretherapy/entry	30	37
Inability to determine bacteriological outcome at posttherapy/TOC	6	4
Total included in PPb analysis	72	76

Note: A subject may have had more than one reason for exclusion or major protocol violation.
Sponsor's Table

Demographics and pretherapy/entry characteristics – mITT population

Characteristic	Number of subjects (%) TEL 5-day	CLA 10-day
Total mITT subjects	270	282
Sex		
Male N (%)	144 (53.3)	150 (53.2)
Female N (%)	126 (46.7)	132 (46.8)
Age (years)		
Median (range) years	62 (19-92)	61 (18-95)

<65 years N (%)	161 (59.6)	165 (58.5)
≥65 years N (%)	109 (40.4)	117 (41.5)
BMI (kg/m^2) N	268	280
Mean ± SD	27.0 ± 6.1	27.1 ± 6.4
Weight (kg) N	270	281
Mean ± SD	76.3 ±19.2	76.3 ± 19.9
Race		
White N (%)	258 (95.6)	266 (94.3)
Black N (%)	8 (3.0)	10 (3.5)
Asian/Oriental N (%)	1 (0.4)	1 (0.4)
Multiracial N (%)	3 (1.1)	5 (1.8)
Smoking status		
Smoker	113 (41.9%)	112 (39.7%)
Ex-smoker	118 (43.7%)	115 (40.8%)
Non-smoker	39 (14.4%)	55 (19.5%)

Sponsor's Table

Statistical Reviewer's Comments:

Based on the sponsor's table, demographic and pre-therapy/entry characteristics of the bmITT population, there are more males (53%) than the females (47%). Median age of the study populations were 62 and 61 years in each treatment groups and ranged from 18 to 95 years in both the groups. Majority of the subjects were white (96% and 94% in each treatment group compared to blacks of 8% and 10 %. There were no significant differences between the two study groups based on their demographic characteristics.

Efficacy Results

Table 37: Clinical outcome at TOC – PPc population

	Number of subjects (%)		
Assessment	**TEL 5-day** n=225	**CLA 10-day** n=231	**95% CI**
Cure	193 (85.8%)	206 (89.2%)	[-10.0; 3.1]
Failure	32 (14.2%)	25 (10.8%)	

TEL = telithromycin, CLA = clarithromycin

Statistical Reviewer's Comments:

Based on the 20% random sample review of the CRFs, the Medical officer had found two subjects (#1070-007 and #1070-002) unevaluable since they did not have the baseline disease characteristics for chronic bronchitis. The sponsor's results would be accepted since the difference in assessment is within acceptable range for this specific submission.

In the PPc population, the clinical cure rates at posttherapy/TOC were 193/225 (85.8%) in the telithromycin 5-day group and 206/231(89.2%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-10.0, 3.1) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

Table 38: Clinical outcome at TOC – PPb population

	Number of subjects (%)		
Assessment	**TEL 5-day**	**CLA 10-day**	**95% CI**
	n=72	n=76	
Cure	59 (81.9%)	66 (86.8%)	[-17.9; 8.1]
Failure	13 (18.1%)	10 (13.2%)	

TEL = telithromycin, CLA = clarithromycin

Statistical Reviewer's Comments:

In the PPb population, the clinical cure rates at posttherapy/TOC were 59/72(81.9%) in the telithromycin 5-day group and 66/76(86.8%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-17.9, 8.1) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%. Note that the number of subjects in each group is small.

Table 39: Clinical outcome at TOC – mITT population

	Number of subjects (%)		
Assessment	**TEL 5-day**	**CLA 10-day**	**95% CI**
	n=270	n=282	
Cure	224 (83.0%)	236 (83.7%)	[-7.3, 5.9]
Failure	46 (17.0%)	46 (16.3%)	

TEL = telithromycin, CLA = clarithromycin

Statistical Reviewer's Comments:

In the mITT population, the clinical cure rates at posttherapy/TOC were 224/270(83.0%) in the telithromycin 5-day group and 236/282(83.7%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-7.3, 5.9) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

Table 40: Clinical outcome at TOC – ITT population

	Number of subjects (%)		
Assessment	**TEL 5-day**	**CLA 10-day**	**95% CI**
	n=272	n=282	
Cure	224 (83.0%)	236 (83.7%)	[-7.9, 5.3]
Failure	48(17.6%)	46 (16.3%)	

TEL = telithromycin, CLA = clarithromycin

Statistical Reviewer's Comments:

In the ITT population, the clinical cure rates at posttherapy/TOC were 224/272(83.0%) in the telithromycin 5-day group and 236/282(83.7%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-7.9, 5.3) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

Table 41: Bacteriological outcome at TOC – PPb population

	Number of subjects (%)		
Assessment	**TEL 5-day**	**CLA 10-day**	**95% CI**
	n=72	n=76	
Cure (eradication)	59 (81.9%)	63 (82.9%)	[-14.5, 12.7]
Failure	13 (18.1%)	13 (17.1%)	

Statistical Reviewer's Comments:

In the PPb population, the bacteriological cure rates at posttherapy/TOC were 59/72(81.9%) in the telithromycin 5-day group and 63/76(82.9%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-14.5, 12.7) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%. Note that the number of subjects in each group is small.

Table 42: Bacteriological outcome at TOC – MITT population

	Number of subjects (%)		
Assessment	**TEL 5-day**	**CLA 10-day**	**95% CI**
	n=90	n=88	
Cure (eradication)	65 (72.2%)	68 (77.3%)	[-18.9, 8.8]
Failure	25 (27.8%)	20 (22.7%)	

Statistical Reviewer's Comments:

In the bacteriological mITT population, the cure rates at posttherapy/TOC were 65/90(72.2%) in the telithromycin 5-day group and 68/88(77.3%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-18.9, 8.8) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

Table 43: Eradication rates for the main causative pathogens at posttherapy/TOC PPb and bmITT populations

Pathogen [a]	Pathogens eradicated/Total pathogens (eradication rate [b] %)			
	TEL 5-day		CLA 10-day	
PPb population				
Total pathogens	86		91	
All pathogens-posttherapy/TOC	70/86	(81.4%)	78/91	(85.7%)
H. influenzae	27/35	(77.1%)	30/36	(83.3%)
M. catarrhalis	17/19	(89.5%)	17/18	(94.4%)
S. pneumoniae	10/13	(76.9%)	7/7	(100.0%)
S. aureus	2/4	(50.0%)	4/6	(66.7%)
bmITT population				
Total pathogens	107		108	
Evaluable pathogens *c*	95		101	
All pathogens-posttherapy/TOC	78/95	(82.1%)	87/101	(86.1%)
H. influenzae	32/40	(80.0%)	31/37	(83.8%)
M. catarrhalis	19/21	(90.5%)	20/21	(95.2%)
S. pneumoniae	11/14	(78.6%)	9/9	(100.0%)
S. aureus	2/4	(50.0%)	5/7	(71.4%)

[a] Single and multiple pathogen infections
[b] Eradication includes both documented and presumed eradication
[c] Denominators based on pathogens from posttherapy/TOC evaluable subjects in bmITT population (i.e., excludes subjects with indeterminate bacteriological outcome).
Sponsor's Table

Statistical Reviewer's Comments:

The 3 common pathogens identified in this study were Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pneumoniae (based on MO's analysis). The applicant is seeking for S. aureus in their proposed label. However, based on MO's analysis, there were few (4/6) isolates and do not provide enough evidence for S. aureus. In the PPb population, for Haemophilus influenzae, the eradication rate for Clarithromycin arm (83%) is higher than Telithromycin arm (77%) and similar conclusions were drawn for Moraxella catarrhalis, Streptococcus pneumoniae and S aureus (Table 43).

In the previuos submission (for trials 3003 and 3007 combined), for the major respiratory pathogens including Streptococcus pneumoniae,13/14(93%), Haemophilus influenzae, 15/25 (60%) and Moraxella catarrhalis, 10/10(100%) were found to be insufficient in numbers.

Overall Evidence based on all three AECB trials:

Table 44: AECB: Clinical cure rates at post-therapy/TOC by pathogen in telithromycin-treated subjects-PPb

Causative pathogen	Previous Studies[a]			New Study (3013)			All AECB		
	N	n	(%)	N	n	(%)	N	n	(%)
S. pneumoniae	14	13	(92.9)	13	10	(76.9)	27	23	(85.2)
H. influenzae	25	15	(60.0)	35	27	(77.1)	60	42	(70.0)
β-lactamase positive	7	3	(42.8)	3	2	(66.7)	10	5	(50.0)
M. catarrhalis	10	10	(100)	19	17	(89.5)	29	27	(93.1)
β-lactamase positive	7	7	(100)	13	11	(84.6)	20	18	(90.0)
Other	21	16	(76.2)	19	16	(84.2)	40	32	(80.0)
Total (all pathogens)	70	54	(77.1)	86	70	(81.4)	156	124	(79.5)

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry; n = number clinically cured
Other = includes organisms recovered in culture from sputum meeting the definition of adequate and identified by the investigator as causative, but which may or may not be generally recognized as pathogenic in subjects with this type of infection. [a]Includes controlled AECB Studies 3003 (vs. amoxicillin-clavulanic acid) and 3007 (vs. cefuroxime axetil).
Sponsor's Table

Statistical Reviewer's Comments:

In this submission (for trials 3003, 3007 and 3013), the bacteriological eradication rates among the PP population for the major respiratory pathogens including Streptococcus pneumoniae,23/27(85.2%), Haemophilus influenzae, 42/60 (70%) and Moraxella catarrhalis, 27/29(93.1%). There were 10 β-lactamase positive H. influenzae isolates identified and 5 of them were clinical and bacteriological cures. Based on the additional study, it did not add any significant number of isloates for β-lactamase positive H. influenzae compared to the previous submission. Also, based on the discussions with MO, in the general population, the current incidence rate in the US is about 40% for these isolates (in all communicated respiratory infections). These studies with the limited number of isolates don't provide any strong evidence.

Table 45: Clinical Cure Rate at Posttherapy/TOC visit –PPc population

Controlled Studies	Clinical Cure Rate				
	KETEK	Comparator	KETEK	Comparator	95 % CI (2-sided)
Study 3003 KETEK (5 day therapy) vs. amoxicillin/clavulanic acid 500/125	99/115	92/112	86.1%	82.1%	[-6.4;14.3]

mg TID (10 day therapy)					
Study 3007 KETEK (5 day therapy) vs.cefuroxime axetil 500mg BID (10 day therapy)	121/140	118/142	86.4%	83.1%	[-5.8;12.4]
Study 3013 KETEK (5 day therapy) vs. clarithromycin 500mg BID (10 day therapy)	193/225	206/231	85.8%	89.2%	[-10.0;3.1]

MO's Table

Statistical Reviewer's Comments:

Comparing all three AECB trials, in the Clinical PP test of cure population, the clinical cure rates were; Study 3003: 86.1% in the Ketek group and 82.1% in the amoxicillin/clavulanic acid 500/125 group with a 95% CI of (-6.4;14.3); Study 3007: 86.4% in the Ketek group and 83.1% in the cefuroxime axetil 500mg group with a 95% CI of (-5.8;12.4); Study 3013: 85.8% in the Ketek group and 89.2% in the clarithromycin 500mg group with a 95% CI of (-10.0;3.1). Based on these results, it can be concluded that the clinical efficacy of Ketek was at least as good as the comparators (amoxicillin/clavulanic acid, cefuroxime axetil, and clarithromycin) given for 10 days in patients with mild to moderate AECB infections, using a non-inferiority margin of 10%.

Table 46: Clinical Cure Rate at Posttherapy/TOC visit –mITT population

Controlled Studies	Clinical Cure Rate				
	KETEK	Comparator	KETEK	Comparator	95 % CI (2-sided)
Study 3003: KETEK (5 day therapy) vs. amoxicillin /clavulanic acid 500/125 mg TID (10 day therapy)	130/160	125/160	81.3%	78.1%	[-6.3;12.6]
Study 3007: KETEK (5 day therapy) vs.cefuroxime axetil 500mg BID (10 day therapy)	142/182	138/191	78.0%	72.3%	[-3.5;15.1]
Study 3013: KETEK (5 day therapy) vs. clarithromycin 500mg BID (10 day therapy)	224/270	236/282	83.0%	83.7%	[-7.3; 5.9]

MO's Table

Statistical Reviewer's Comments:

In the Modified MITT population, the clinical cure rates were; Study 3003: 81.3% in the Ketek group and 78.1% in the amoxicillin/clavulanic acid 500/125 group with a 95% CI of (-6.3;12.6); Study 3007: 78.0% in the Ketek group and 72.3% in the cefuroxime axetil 500mg group with a 95% CI of (-3.5;15.1); Study 3013: 83.0% in the Ketek group and 83.7% in the clarithromycin 500mg group with a 95% CI of (-7.3;5.9). The clinical cure rates in Study 3007 was slightly lower compared to other two studies. Based on these results, it can be concluded that Ketek was equivalent to its comparators (amoxicillin /clavulanic acid, cefuroxime axetil,and clarithromycin), using a non-inferiority margin of 10%.

SAFETY

A detailed safety analysis will be provided by the Medical Officer/Safety Reviewer.

Conclusions and Recommendations

The clinical cure rates in the PPc population at posttherapy/TOC were 193/225 (85.8%) in the telithromycin 5-day group and 206/231(89.2%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-10.0, 3.1) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

The clinical cure rates in the mITT population at posttherapy/TOC were 224/270(83.0%) in the telithromycin 5-day group and 236/282(83.7%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-7.3, 5.9) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%. The ITT results were similar and concur with the MITT conclusions.

The bacteriological cure rates in the PPb population at posttherapy/TOC were 59/72(81.9%) in the telithromycin 5-day group and 63/76(82.9%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-14.5, 12.7) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%. Note that the number of subjects in each group is small.

The bacteriological cure rates in the mITT population at posttherapy/TOC were 65/90(72.2%) in the telithromycin 5-day group and 68/88(77.3%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-18.9, 8.8) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

In the PPb population at TOC, the eradication rates for Clarithromycin arm was higher than Telithromycin arm for *Haemophilus influenzae:* telithromycin 5-day 77.1% (27/35) and clarithromycin 10-day 83.3% (30/36), *Moraxella catarrhalis:* telithromycin 5-day 89.5% (17/19) and clarithromycin 10-day 94.4% (17/18), and *Streptococcus pneumoniae:* telithromycin 5-day 76.9% (10/13) and clarithromycin 10-day 100% (7/7), although the number of isolates were small.

Comparing all three AECB trials, in the Clinical PP test of cure population, the clinical cure rates were; Study 3003: 86.1% in the Ketek group and 82.1% in the amoxicillin/clavulanic acid 500/125 group with a 95% CI of (-6.4;14.3); Study 3007: 86.4% in the Ketek group and 83.1% in the cefuroxime axetil 500mg group with a 95% CI of (-5.8;12.4); Study 3013: 85.8% in the Ketek

group and 89.2% in the clarithromycin 500mg group with a 95% CI of (-10.0;3.1). Based on these results, it can be concluded that the clinical efficacy of Ketek was at least as good as the comparators (amoxicillin/clavulanic acid, cefuroxime axetil, and clarithromycin) given for 10 days in patients with mild to moderate AECB infections, using a non-inferiority margin of 10%.

In the Modified MITT population, the clinical cure rates were; Study 3003: 81.3% in the Ketek group and 78.1% in the amoxicillin/clavulanic acid 500/125 group with a 95% CI of (-6.3;12.6); Study 3007: 78.0% in the Ketek group and 72.3% in the cefuroxime axetil 500mg group with a 95% CI of (-3.5;15.1); Study 3013: 83.0% in the Ketek group and 83.7% in the clarithromycin 500mg group with a 95% CI of (-7.3;5.9). Based on these results, it can be concluded that Ketek was equivalent to its comparators (amoxicillin /clavulanic acid, cefuroxime axetil,and clarithromycin), using a non-inferiority margin of 10%.

Overall, the clinical efficacy of Telithromycin was at least as good as the comparators (amoxicillin /clavulanic acid, cefuroxime axetil, and clarithromycin) in patients with mild to moderate AECB infections. The cure rates were not high enough to rule out any reasonable placebo effect, had there been a placebo arm and no scientific basis could be provided for the conclusion. However, for the major respiratory pathogens leading to AECB including S. *Pneumonia*, H. *Influenzae* and M. *Catarrhalis,* the evidence is not strong enough to make any statistically meaningful conclusions.

2.4 Statistical and Technical Issues

In all these studies testing the equivalence of treatment differences with respect to the efficacy variables were assessed based on a two-tailed 95% confidence interval (if there are no multiplicity adjustment issues) of the difference in clinical and microbiological cure rates. The robustness of the primary efficacy results was assessed using the PP and the ITT and/or the MITT (or bMITT) populations.

The primary efficacy analyses for CAP (study 4003) and AECB (3013) was evaluated using a non-inferiority margin (delta) of 10%. However, for AECB, according to the reviewer, there was no scientific basis for choosing a higher delta of 10% without knowing the actual placebo effect. If there had been a placebo arm, we could have better estimated the efficacy of this drug for this indication.

For CAP study 4003, testing the equivalence of the treatment differences was assessed using a two-tailed 97.5% confidence interval adjusting multiplicity. This study was a multicenter, double-blinded, active-controlled, three-arm parallel-group (1:1:1) comparative study of telithromycin (800 mg given once daily) for 5 days versus 7 days versus 10 days of oral clarithromycin (500 mg given twice daily).

2.5 Conclusions and Recommendations

1. Community Acquired Pneumoniae:

This review was only focused on 2 new additional studies (4003 and 3012) in subjects with CAP to provide additional efficacy data.

Study 4003: Among the Clinical Per Protocol (PPc) patients, the clinical cure rates at the Follow-

Up Visit were; Telithromycin 5-day: 89.3% (142/159 subjects); Telithromycin 7-day: 88.8% (143/161 subjects); and Clarithromycin 10-day: 91.8% (134/146 subjects). The 97.5% CI (-10.0, 5.0) for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days) and Telithromycin 800 mg once daily (for 7 days) was marginally equivalent (97.5% CI: -10.5, 4.6) to Clarithromycin 500 mg, using a non-inferiority margin of 10%.

Among the MITT patients, the clinical cure rates at the Follow-Up Visit were; Telithromycin 5-day: 82.4% (154/187 subjects); Telithromycin 7-day: 82.2% (157/191 subjects); and Clarithromycin 10-day: 81.2% (147/181 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was equivalent (97.5% CI for 5-days: -7.9, 10.2; 7-days: -8.5, 10.5) to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

Bacteriological cure rates at the Follow-Up Visit among evaluable patients (PPb) were; telithromycin 5-day: 87.7% (57/65 subjects); telithromycin 7-day: 80.0% (52/65 subjects); and clarithromycin 10-day: 83.3% (45/54 subjects). The 97.5% CI for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was not equivalent (97.5% CI for 5 days: -11.9, 20.6; 7-days: -20.9, 14.3) to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%. Note that the number of subjects were small in each treatment group.

Bacteriological cure rates at the Follow-Up Visit among bacteriological mITT patients were; telithromycin 5-day: 80.2% (89/111 subjects); telithromycin 7-day: 76.4% (94/123 subjects); clarithromycin 10-day: 73.5% (75/102 subjects). The 97.5% CI (-7.2, 20.5) for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent and Telithromycin 800 mg once daily (for 7 days) was not equivalent (97.5% CI: -11.0, 16.8) to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

Study 3012: In this open label trial, at posttherapy/TOC in the PPc population, the clinical cure rate was 424/473(89.6%, 95%CI: 86.8, 92.4). In the mITT population, the clinical cure rate was 447/538(83.1%, 95%CI: 79.9, 86.3). The clinical cure rate was dropped by 6.5% even though there were 65 more subjects in the mITT population.

The microbiologic cure (eradication) rate at the posttherapy/TOC Visit among the PPb patients was 161/179(89.9%, 95%CI: 85.5, 94.3) and in the bmITT population, microbiological eradication rate was 229/265(86.4%, 95%CI: 82.2, 90.5).

For Streptococcus pneumoniae, the eradication rate at the posttherapy/TOC visit in the PPb population was 96.7% and the eradication rate for Haemophilus influenzae was 90.5%. Similar rates were reported in the MITT population.

2. Infections due to Drug-Resistant *Streptococcus pneumoniae:*

The efficacy of the treatment for infections due to drug-resistant *streptococus pneumonia* was reviewed for the indications of CAP and ABS.

a) Community Acquired Pneumoniae: In this review, the efficacy of infections due to drug-resistant *S. pneumoniae* isolates in CAP was performed based on the data from studies 3000, 3001. 3006, 3009OL, 3010, 3012 and 4003. The two Japanese studies, 3107 (new) and 2105 were evaluated separately for additional evidence.

In the PP population, there were 19 isolates with Penicillin G-resistant S. pneumoniae, of which 16/19 (84.2%, 95% CI: 60.4, 96.6) were clinical cures and in the MITT population, there were 28 isolates with Penicillin G-resistant S. pneumoniae, of which 19/28 (67.9%, 95% CI: 47.6, 84.1) were clinical cures. Similar bacteriological cure rates were observed in the PP population. The cure rates in the MITT population was considerably low compared to PP population. Based on the sponsor's results, of the nine additonal patients in the MITT, 4 of them had an fine score of 3 or greater. The numbers of isolates were too small to draw any statistically meaningful conclusion.

In the PP population, among the 29 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, of which 25/29 (86.2%, 95% CI: 68.3, 96.1) were clinical cures and in the MITT population, of the 37 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, 29/37 (78.4%, 95% CI: 61.8, 90.2) were clinical cures.

The cure rates among the subjects with both PRSP and ERSP isolates were; 8/11 (73%) in the PP and 10/16 (62.5%) in the MITT populations.

Among the bacteremic patients due to PRSP, the clinical cure rate was 5/7(71.4%) in the PP population and 5/10 (50%) in the MITT population. For bacteremia due to ERSP, the clinical cure rate was 8/10 in the PP and 8/11 in the MITT populations.

Based on the Japanese studies, subjects with S. pneumoniae isolates resistant to penicillin G and/or erythromycin A, in the PP population among those with PRSP and ERSP, there were 8/8 clinical and bacteriological cures. Among the 21 macrolide- (erythromycin A-) resistant S. pneumoniae, 19/21(90.5%, CI: 69.6, 98.8) were clinical and bacteriological cures. There were no bacteremic patients in this group.

Overall, there is no substantial evidence available in support of the efficacy of this drug in the treatment of CAP due to PRSP or ERSP isolates. There were limited numbers of bacteremic patients with relatively low success rates.

b) Acute Bacterial Sinusitis: In this review of efficacy, *Streptococcus pneumoniae* isolates resistant to penicillin G and/or erythromycin A (macrolides) were analyzed based on the previously submitted studies (studies 3002, 3005 and 3011). All the isolates are pooled together and the results are as follows:

In the bacteriological PP population, there were 13 isolates with Penicillin G-resistant S. pneumoniae, of which 11/13 (84.6%, 95% CI:54.6,98.1) were clinical and bacteriological cures and in the MITT population, there were 16 isolates with Penicillin G-resistant S. pneumoniae, of which 14/16 (87.5%, 95%CI:61.7, 98.4) were clinical and bacteriological cures. The cure rates among the subjects with both PRSP and ERSP isolates in the PP and MITT were 9/11(73%) and 11/13 (85%) respectively.

Among the 21 isolates in the PP population with macrolide- (erythromycin A-) resistant S. pneumoniae, 18/21 (85.7%, 95%CI: 63.7, 97.0), were clinical and microbiological cures. Among the 26 isolates in the MITT population, 21/26 (80.8%, 95% CI:60.6, 93.4) were cures.

Overall, based on the data submitted, there is not enough evidence to support the claim for PRSP or ERSP. Since the applicant has requested for 5-day treatment of sinusitis with telithromycin, there were only 10 patients with PRSP and 14 patients with ERSP. In the PP population, the clinical cure rate was 8/10 (80%) for PRSP and 12/14 (86%) for ERSP. The evidence is substantially low due to smaller number of isolates and it is difficult to draw any statistically meaningful conclusion.

3. Acute Exacerbation of Chronic Bronchitis (AECB):

There were three studies (3003, 3007 and 3013) submitted in the treatment of patients with acute bacterial exacerbation of chronic bronchitis (AECB) and this review was focused on study of 3013 and the results are as follows:

The clinical cure rates in the PPc population at posttherapy/TOC were 193/225 (85.8%) in the telithromycin 5-day group and 206/231(89.2%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-10.0, 3.1) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

The clinical cure rates in the mITT population at posttherapy/TOC were 224/270(83.0%) in the telithromycin 5-day group and 236/282(83.7%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-7.3, 5.9) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%. The ITT results were similar and concur with the MITT conclusions.

The bacteriological cure rates in the PPb population at posttherapy/TOC were 59/72(81.9%) in the telithromycin 5-day group and 63/76(82.9%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-14.5, 12.7) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%. Note that the number of subjects in each group is small.

The bacteriological cure rates in the mITT population at posttherapy/TOC were 65/90(72.2%) in the telithromycin 5-day group and 68/88(77.3%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-18.9, 8.8) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

In the PPb population at TOC, the eradication rates for Clarithromycin arm was higher than Telithromycin arm for *Haemophilus influenzae:* telithromycin 5-day 77.1% (27/35) and clarithromycin 10-day 83.3% (30/36), *Moraxella catarrhalis:* telithromycin 5-day 89.5% (17/19) and clarithromycin 10-day 94.4% (17/18), and *Streptococcus pneumoniae:* telithromycin 5-day 76.9% (10/13) and clarithromycin 10-day 100% (7/7), although the number of isolates were small.

Comparing all three AECB trials, in the Clinical PP test of cure population, the clinical cure rates were; Study 3003: 86.1% in the Ketek group and 82.1% in the amoxicillin/clavulanic acid 500/125 group with a 95% CI of (-6.4;14.3); Study 3007: 86.4% in the Ketek group and 83.1% in the cefuroxime axetil 500mg group with a 95% CI of (-5.8;12.4); Study 3013: 85.8% in the Ketek group and 89.2% in the clarithromycin 500mg group with a 95% CI of (-10.0;3.1). Based on these results, it can be concluded that the clinical efficacy of Ketek was at least as good as the comparators (amoxicillin/clavulanic acid, cefuroxime axetil, and clarithromycin) given for 10 days in patients with mild to moderate AECB infections, using a non-inferiority margin of 10%.

In the Modified MITT population, the clinical cure rates were; Study 3003: 81.3% in the Ketek group and 78.1% in the amoxicillin/clavulanic acid 500/125 mg group with a 95% CI of (-6.3;12.6); Study 3007: 78.0% in the Ketek group and 72.3% in the cefuroxime axetil 500mg group with a 95% CI of (-3.5;15.1); Study 3013: 83.0% in the Ketek group and 83.7% in the clarithromycin 500mg group with a 95% CI of (-7.3;5.9). Based on these results, it can be concluded that Ketek was equivalent to its comparators (amoxicillin /clavulanic acid, cefuroxime axetil,and clarithromycin), using a non-inferiority margin of 10%.

Based on the data provided, the clinical efficacy of Telithromycin was at least as good as the comparators in patients with mild to moderate AECB infections although the true placebo effect for this drug is unknown. However, for the major respiratory pathogens leading to AECB including S. *Pneumonia*, H. *Influenzae* and M. *Catarrhalis,* the evidence was not strong enough to draw any statistically meaningful conclusion.

Overall, the approval of this drug should depend upon the evidence provided on Safety and efficacy. This review was only focused on the efficacy based on study 3013, although the results from the previous trials were provided for additional evidence. For conclusions and recommendations on overall safety and efficacy, refer to reviews from Dr. George Rochester and other medical officers.

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Thamban Valappil, Ph.D.
Mathematical Statistician, DOBIII

Concur: _____
Daphne Lin, Ph.D., Team Leader, DOBIII

HFD-520/DivDir/Dr. Soreth
HFD-520/DepDivDir/Dr. Gavrilovich
HFD-520/Team Leader/Dr. Ross
HFD-520/Team Leader/Dr. Alexander
HFD-520/MedicalReviewer/Dr. Davidson
HFD-47/DSI/Dr. Khin
HFD-725/OB/DepDir/Dr. Anello
HFD-725/DivDir/Dr. Huque
HFD-725/BiometricsTeamLeader/Dr. Lin
HFD-725/BiometricsReviewer/Dr. Valappil
HFD-520/ProjMan/Mrs. Judit Milstein

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Thamban Valappil
12/20/02 10:14:33 AM
BIOMETRICS

Daphne Lin
12/20/02 10:25:13 AM
BIOMETRICS

Statistical Review and Evaluation

NDA Number:	21-144
Generic Drug Name:	telithromycin®
Drug Trade Name:	KETEK™
Formulation:	400 mg tablets
Applicant:	Aventis Pharmaceuticals, Inc.
Indications:	1. Acute Maxillary Sinusitis (AMS) 2. Acute Exacerbation of Chronic Bronchitis (AECB) 3. Group A Beta-Hemolytic (GABHS) Pharyngitis/Tonsillitis (T/P) 4. Community Acquired Pneumonia (CAP)
Documents Reviewed:	Vol. 1.1-1.3, 1.272-1.539, Major Clinical Amendment
Submission Date:	February 28, 2000
PDUFA Date:	May 28, 2001
Major Amendment	February 28, 2001
Date Review Completed	May 25, 2001
Type of Review:	Clinical/Statistical
Statistical Reviewer:	G. Rochester, PhD, HFD-725
Clinical Reviewer:	A. Davidson, MD, HFD-520 (CAP, AECB) M. Makhene, MD, MPH, HFD-520 (T/P) N. Moledina, MD, HFD-520 (AMS)
Project Manager:	J. Cintrón, MA, RPh, HFD-520

EXECUTIVE SUMMARY and RECOMMENDATIONS

The registration dossier for telithromycin® (KETEK™) presents efficacy and safety data from 10 double-blind, multi-center, multi-national, randomized, parallel group, phase III clinical trials (9 of these trials included an non-telithromycin, active-control arm) and 3 open label supportive clinical studies. While some studies included patients from the US, there were no studies which enrolled US patients only. There were at least 2 comparative trials for each indication. The sponsor requested approval for the following four indications:

1. Community-acquired pneumonia (CAP)
2. Acute bacterial exacerbation of chronic bronchitis (AECB)
3. Acute bacterial maxillary sinusitis (AMS)
4. Group A Beta-Hemolytic Streptococci (GABHS) tonsillitis/pharyngitis (T/P)

Community-acquired pneumonia

There were 6 phase III clinical trials conducted for the CAP indication: 3 comparative (protocols 3001, 3006 and 3009) and 3 open label (protocols 3000, 3009OL and 3010). All studies used a dose of 800 mg oral telithromycin daily for dosing regimens of 7 to 10 days.

Telithromycin 800 mg was administered to 1373 subjects with CAP. Telithromycin given orally at 800 mg once daily for 10 days was equivalent in clinical efficacy at posttherapy/TOC to clarithromycin given orally at 500 mg bid for 10 days (Study 3006) and amoxicillin given orally 1000 mg tid for 10 days (Study 3001) in the treatment of adult subjects with CAP. In Study 3009, clinical cure rates were >90% for both telithromycin (800 mg orally once a day for 7-10 days) and trovafloxacin (200 mg orally once daily for 7-10 days). In all studies, results in the mITT populations were consistent with the results observed in the PPc population.

Telithromycin showed similar efficacy in subgroups of interest with cure rates of over 90% in study subjects with an increased risk of morbidity, such as subjects >65 years of age, Fine score ≥III, and subjects with documented pneumococcal bacteremia (43/47 subjects), and diagnosis of atypical pathogens: *Legionella pneumophila* 100% (12/12 subjects), *Mycoplasma pneumoniae* 96.8% (30/31 subjects), and *Chlamydia pneumonia* 94.1% (32/34 subjects). While the bacteriologic activity of telithromycin against the pathogens of interest for empiric therapy in treating upper respiratory infections appears to show efficacy these are sparse data except for the penicillin G. sensitive *S. pneumoniae*. Overall, the body of bacteriologic evidence on which the grant a claim for resistant pathogens is minimal.

Acute exacerbation of chronic bronchitis

Telithromycin 800 mg once daily for 5 days was shown to be equivalent in clinical efficacy to cefuroxime axetil given for 10 days, and was similar to amoxicillin/clavulanic acid given for 10 days in subjects with AECB of mild to moderate severity. Bacteriological eradication and clinical cure rates by pathogen were satisfactory in telithromycin-treated subjects for *S. pneumoniae 93%* (13/14), *H. influenzae 60%* (15/25), and *M. catarrhalis* 100% (10/10). These constitute very few pathogens from which to conclude bacteriological efficacy although telithromycin appears to show some efficacy with respect to the main pathogens of interest except for *H. influenzae* in subjects with AECB.

Acute maxillary sinusitis

Telithromycin 800 mg given orally once daily for 5 days or 10 days were similar in clinical efficacy at posttherapy/TOC (telithromycin 5-d: 91.1%; telithromycin 10-d: 91.0%) in the PPc population (study 3002). In the mITT population the telithromycin 5-day regimen demonstrated approximately 5% lower clinical cure rate compared to the telithromycin 10-day regimen (telithromycin 5-d: 82.6%; telithromycin 10-d: 87.5%). The mITT population did not attain a –10% lower bound of the 95% C.I. for the difference in cure rates (-13.1%; 3.3%). Given that this trial did not include a non-telithromycin comparator arm the cure rates may be subject to the potential biases that may occur in open label studies.

Study 3005 compared both telithromycin 5-d and 10-day with amoxicillin/clavulinic acid. This study provided estimates of clinical cure rates of (telithromycin 5-d: 75.3%; telithromycin 10-d: 72.9%; amoxicillin/ clavulinic acid: 74.5%) in the PPc population. The results in the mITT population were similar for all 3 treatment groups (telithromycin 5-d: 69.7%; telithromycin 10-d: 68.6%; amoxicillin/clavulinic acid: 68.3%). The clinical cure rates from this study are appreciably lower than those seen in Study 3002. No clear explanation for this difference is postulated at this time.

Study 3011 compared telithromycin 5-d to cefuroxime axetil. The clinical cure rates were (telithromycin 5-d: 85.2%; cefuroxime axetil: 82.0%) in the PPc population and (telithromycin 5-d: 80.4%; cefuroxime axetil: 72.4%) in the mITT population. The case definition for this study limited enrollment to subjects with >7 day of symptoms, the period when the probability of infection due to a non-bacterial etiology is high. The results in the PPc and mITT populations support a conclusion of therapeutic equivalence of telithromycin 5-d and cefuroxime axetil.

For the three main pathogens which are generally considered important for empiric therapy in acute bacterial sinusitis management the clinical cure rates for telithromycin 5-d were: *S. pneumoniae* 90.2% (55/61); *M. catarrhalis* 92.9% (13/14) and *H. influenzae* 87.5% (42/48). When only single pathogen infections are considered, 6/8 of *S. pneumoniae* resistant to penicillin G and 8/10 of *S. pneumoniae* resistant to erythromycin A were clinically cured in the PPb population at posttherapy TOC. The bacteriologic data are minimal.

Group A beta-hemolytic streptococcal tonsillitis/pharyngitis

Telithromycin 800 mg given orally once a day for 5 days in subjects with Group A Beta-hemolytic streptococcal *(S. pyogenes)* tonsillitis/pharyngitis was 5% lower in clinical and bacteriological efficacy to 10 days of penicillin VK, the standard first line therapy for this indication. Telithromycin 5-d appears to be therapeutically equivalent to 10 days of clarithromycin, the standard therapy for subjects allergic to beta-lactams. Eradication of *S. pyogenes* with telithromycin 5 days was similar to 10 days of treatment with penicillin VK and 10 days of treatment with clarithromycin at the late posttherapy visit (LPTV).

In tonsillitis/pharyngitis studies due to GABHS among adults, telithromycin 800 mg given orally once a day for 5 days was not equivalent in clinical and bacteriological efficacy to 10 days of penicillin VK, the standard first line therapy for this indication. It also barely achieved the minimum threshold cure rate expected of first line anti-infective therapies for GABHS tonsillitis/pharyngitis. Telithromycin did show clinical and microbiologic equivalence to 10 days of clarithromycin. Telithromycin was effective in the treatment of tonsillitis/pharyngitis infection due to penicillin sensitive *S. pyogenes*.

Recommendations

Merely achieving the statistical criterion of achieving a non-inferiority lower bound for declaring therapeutic equivalence of telithromycin to comparators does not guarantee a win for any drug. Purely from a point or view of clinical and bacteriologic efficacy telithromycin demonstrated efficacy in the treatment of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute bacterial maxillary sinusitis. The bacteriologic data are sparse throughout except for penicillin susceptible *S. pneumoniae*. Telithromycin demonstrated good eradication rates against penicillin susceptible *S. pneumoniae*, *M. catarrhalis* and *H. influenzae*, the pathogens which are important in empiric management of these three respiratory tract infections. Telithromycin was equivalent to clarithromycin in the treatment of group A. beta-hemolytic streptococcal tonsillitis/pharyngitis infection in adults. Data on S. pneumoniae, which are resistant to penicillin G and/or erythromycin A are sparse and may not be adequate to grant a label at this time. Telithromycin may have a role in treating respiratory tract infections in subjects with either penicillin G and/or erythomycin A resistant *S. pneumoniae*, however the data are limited at this time. Based solely on efficacy telithromycin is approvable for the indications requested. However, the safety profile of the drug, the type and severity of infections that are under consideration further characterization of the risks associated with this drug is advisable prior to approval. See safety review for details regarding risks and benefits.

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1 INTRODUCTION

The registration dossier for telithromycin® (KETEK™) presents efficacy and safety data from 10 double-blind, multi-center, multi-national, randomized, parallel group, phase III clinical trials (9 of these trials included an non-telithromycin, active-control arm) and 3 open label supportive clinical studies. While some studies included patients from the US, there were no studies which enrolled US patients only. There were at least 2 comparative trials for each indication as shown in Table 1.1. Whenever the comparator arm(s) had a different duration of therapy or dosing regimen than the regimen used for telithromycin placebo was utilized to mask the treatment for all controlled double-blind trials (see section 3.4). The sponsor requested approval for the following four indications:

1. Community-acquired pneumonia (CAP)
2. Acute bacterial exacerbation of chronic bronchitis (AECB)
3. Acute bacterial maxillary sinusitis (AMS)
4. Group A Beta-Hemolytic Streptococci (GABHS) Tonsillitis/Pharyngitis (T/P)

Table 1.1. Phase III clinical trials conducted to demonstrate the efficacy and safety of 800 mg oral telithromycin for the four indications

Indication / Study number	Design	Treatment Regimen	
		Telithromycin	Comparators
CAP			
3000 (Europe)	Open label	7–10 days	None
3001 (Europe)	Double blind, randomized, active controlled, 2 arm, parallel group	10 days	Amoxicillin 1000 mg PO tid x 10 days
3006(US+)	Double blind, randomized, active controlled, 2-arm, parallel group	10 days	Clarithromycin 500 mg bid PO x 10 days
3009 (US+)	Double blind, randomized, active controlled, 2-arm, parallel group	7-10 days	Trovofloxacin 200 mg QD PO x 7-10 days
3009OL (US+)	Open label	7-10 days	None
3010 (US+)	Open label	7 days	None
AECB			
3003 (Europe)	Double blind, randomized, active controlled, 2-arm, parallel group	5 days	Amoxicillin/clavulanic acid 500/125 mg PO tid x 10 days
3007 (US+)	Double blind, randomized, active controlled, 2-arm, parallel group	5 days	Cefuroxime axetil 500 mg PO tid x 10 days
Sinusitis			
3002 (Europe)	Double blind, randomized, 2-arm, telithromycin 5 d vs 10 d, parallel group	5 days	Telithromycin 800 mg PO QD x 10 days
3005 (US+)	Double blind, randomized, active controlled, 3-arm, parallel group	5 days 10 days	Amoxicillin/Clavulanic Acid 500/125 mg PO tid x 10 days
3011 (US+)	Double blind, randomized, active controlled, 2-arm, parallel group	5 days	Cefuroxime axetil 250 mg PO bid x 10 days
Tonsillitis/ Pharyngitis			
3004 (Europe)	Double blind, randomized, active controlled, 2-arm, parallel group	5 days	Penicillin V-K 500 mg bid PO x 10 days
3008 (US+)	Double blind, randomized, active controlled, 2-arm, parallel group	5 days	Clarithromycin 250 mg bid PO x 10 days

The purpose of this report is to summarize and critically evaluate the evidence from the entire phase III clinical studies as submitted by Aventis Pharmaceuticals, Inc., with respect to efficacy of telithromycin for the respective indications. Clinical and bacteriological efficacy will be

summarized. Approval of any new drug considers the risks/benefit balance based on factors such as: the indications for which the product is intended, severity and seriousness of the disease, the target population, the robustness of the findings, current treatment options and the safety profile of the new drug.

2 BACKGROUND

2.1 Ketolides

Macrolides are recommended as an alternative treatment of respiratory tract infections (RTIs) of mild and moderate severity among penicillin-allergic patients, and as empirical treatment in adult non-hospitalized patients without significant comorbidity. Erythromycin A does not always demonstrate desirable solubility and acid stability, resulting in reduced bioavailability, unpredictable pharmacokinetics, poor activity at low pH, and rapid degradation in the gastrointestinal tract. The newer macrolides, such as clarithromycin and azithromycin, show better acid stability and improved pharmacokinetics. However, they have the disadvantages of reduced activity at low pH and macrolide cross-resistance.

KETEK™ tablets contain telithromycin, a semisynthetic ketolide representing a new class of 14-membered ring macrolide antibacterials. Chemically, telithromycin is designated as 11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]6-O-ethyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]erythromycin.
Telithromycin differs chemically from the macrolide-azalide group of antibacterials by the substitution of a keto function at position 3 of the macrolactone ring instead of the α-L-cladinose moiety, a sugar thought to possess anti-bacteriologic properties. Telithromycin also possesses an 11-12-carbamate extension. The lack of α-L-cladinose together with the C11-C12 carbamate side chain is believed to confer antimicrobial activity. The empirical formula for KETEK™ is $C_{43}H_{65}N_5O_{10}$.

2.2 Ethics

The clinical study protocols, informed consent document(s), and other appropriate study-related documents were reviewed and approved by independent ethics committees. According to sponsor's documentation these procedures are in accordance with the Good Clinical Trials Practice guidelines, the Helsinki declarations, and the ICH guidelines. Informed consent was obtained prior to the conduct of any study-related procedures.

2.3 Censored Sites

Nine sites were selected for investigation by the Division of Scientific Investigation (DSI). Six sites (4 investigators) failed to meet good clinical trial conduct and the standards for data collection and documentation required by the agency and were therefore censored by the agency from all analyses. Aventis also censored these sites from their analyses. A total of 186 subjects were excluded from all analyses for efficacy and safety from the original submission and 11 patients from the major amendment. Table 2.1 summarizes the number of subjects censored by the FDA from the original NDA application. The distribution of baseline factors for telithromycin and comparators remained similar for all comparative studies. Censoring did not change the conclusions for any trial or indication.

Table 2.1. Subjects censored by the agency from sponsor's original NDA submission[1]

Indication	Study Protocol	Number of subjects		
		Telithromycin	Comparator	Total
CAP	3009	13	12	25
AECB	3007	62	62	124
Sinusitis	3005	26	11	37
Total				186

[1] Eleven (11) additional subjects were censored when the major clinical amendment was submitted because two sites were associated with investigators who were previously censored by the agency.

2.4 Dosing of study drug

2.4.1. Telithromycin

In all the Phase III studies, telithromycin was administered as an oral dose of 800 mg (2 400 mg tablets) once daily. When the telithromycin dosing regimen called for fewer days of active medication than in the comparative treatment group, a regimen of placebo treatment followed up until the maximum number of days of treatment (10 days) required for the comparator in order to maintain the blind.

2.4.2 Active comparators

Comparator dosing regimens (all given orally) were as follows:

- CAP: (comparative studies) comparator regimens were amoxicillin 1000 mg tid for 10 days (Study 3001), clarithromycin 500 mg bid for 10 days (Study 3006), and trovafloxacin 200 mg once daily for 7 to 10 days (Study 3009);
- AECB: comparator regimens were co-administration of amoxicillin/clavulanic acid at 500/125 mg tid for 10 days (Study 3003) and cefuroxime axetil 500 mg bid for 10 days (Study 3007)
- Sinusitis Study 3005, co-administration of amoxicillin/clavulanic acid at 500/125 mg tid for 10 days was used as the comparator, there was no active comparator in Study 3002, which compared two durations of treatment with telithromycin (5 days and 10 days) in a randomized, double-blind design. In Study 3011, cefuroxime axetil 250 mg bid for 10 days was used as the comparator
- Tonsillitis/pharyngitis: comparator regimens were penicillin VK 500 mg tid for 10 days (Study 3004) and clarithromycin 250 mg bid for 10 days (Study 3008).

3 STATISTICAL ASPECTS

3.1 Primary hypotheses

The primary hypotheses for CAP, AECB and sinusitis studies were to demonstrate equivalence of 800 mg oral telithromycin for various dosing regimens of telithromycin (5-days, 7-days, 7-10 days or 10-days) and comparator with respect to clinical efficacy at the designated posttherapy/test-of-cure visit in the clinical per protocol (PPc) and the modified intent-to-treat (mITT) populations. For the tonsillitis/pharyngitis indication the primary efficacy was based on bacteriologic eradication in the per protocol (PP) and bacteriologic mITT (bmITT) population at the designated TOC window. The open label studies aimed to demonstrate the clinical efficacy and safety of 800 mg oral telithromycin and give supportive evidence for the respective indication.

3.2 Analysis populations

Definitions of the various study populations used in the analyses of efficacy are shown in Table 3.1. The definition of the mITT is different from the classic definition of intent-to-treat (i.e., all randomized patients). The decision to analyze mITT instead of ITT for formal analyses was to exclude subjects with a clear misdiagnosis, and to provide a more conservative approach to establish statistical and clinical equivalence between telithromycin and the comparators under study. The difference between the ITT and mITT populations was most commonly attributed to subjects who did not meet the predefined radiologic or microbiologic criteria as specified in the protocol for the infection under study.

Table 3.1. Definitions populations used for the determination of efficacy

mITT	All randomized subjects, as treated, with a confirmed diagnosis of the infection, as defined in the respective study protocol, who received at least one dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and radiologic findings supportive of the diagnosis, as defined in the protocols. This definition was intended to exclude subjects with a clear misdiagnosis, in whom study medication was not expected to demonstrate the desire therapeutic effect.
PPc	All mITT subjects except those with major protocol violations and/or indeterminate responses.
bmITT	All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for infection.
PPb	All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

3.3 Number of subjects and enrollment

A total of 5926 subjects were enrolled and 4998 subjects were randomized (or assigned, as in open-label studies 3000, 3009OL and 3010) to telithromycin (3298 subjects) or comparator drugs (1700 subjects) in the Phase III clinical program. There were 3290 telithromycin treated subjects and 1695 were treated with one of several comparators. Adult subjects (>18 years of age) were to be included in CAP, AECB, and acute sinusitis studies. Adult and adolescents subjects (>13 and <18 years of age) were to be included in the tonsillitis/pharyngitis studies. Subject accounting for the telithromycin-treated subjects is shown in Table 3.2 which excludes those subjects who were censored by the agency. The PPb population is small relative to the mITT population partly because some studies were predominantly clinical and captured few subjects form whom a pathogen was actually obtained.

Table 3.2. Number of telithromycin-treated subjects in the Phase III studies by indication and analysis population

			Population			
Indication	**Randomized**	**Treated**	**mITT**	**PPc**	**bmITT**	**PPb**
CAP	1427	1427	1373	1132	562	344
AECB	346	343	342	255	82	64
Sinusitis	1095	1090	980	731	345	253
Tonsillitis/Pharyngitis	430	430	430	265	325	265
TOTAL	3298	3290	3125	2383	1314	926

Population definitions: mITT = modified intent-to-treat; PPc = clinically evaluable per protocol; bmITT = bacteriologically evaluable modified intent-to-treat; PPb = bacteriologically evaluable patients.

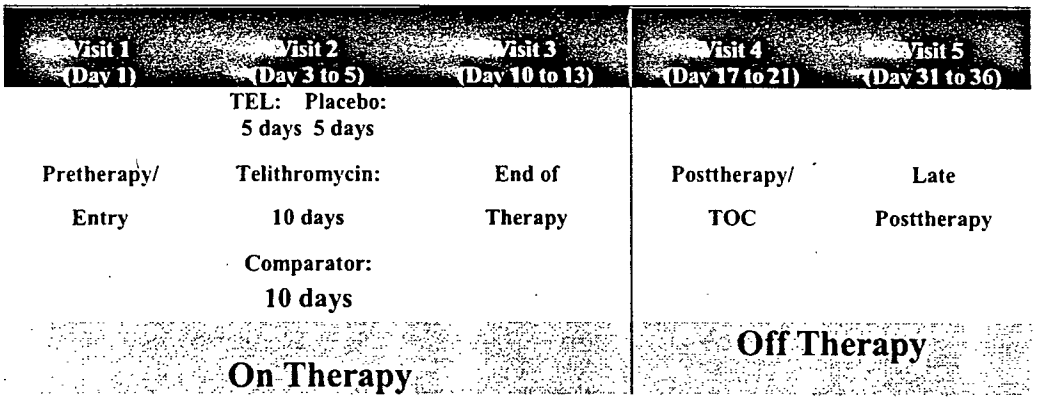
3.4 Study design and assessment of clinical/bacteriologic response

Across all protocols there were five assessment visits as shown in Figure 3.1: (1) a pre-therapy/entry visit (Visit 1, Day 1); (2) an on-therapy visit (Visit 2 , Days 3-5); (3) an end-of-therapy visit (Visit 3, Days 11-13); (4) a test-of-cure visit (Visit 4, Days 17-21); and (5) a late-

post-therapy visit (Visit 5, Days 31-36). Clinical and bacteriologic efficacy were primarily analyzed at the posttherapy/test-of-cure visit in the PPc and mITT populations. Similar time windows were used for these visits in the studies for all four indications. A time window of Days 17-24 (Days 16-23 in tonsillitis/pharyngitis) was used for the assessment of efficacy at test-of-cure. A time window of Days 31-45 was used for the efficacy analyses at late posttherapy. This extended window was used to accommodate the more erratic visit timing at late posttherapy compared to posttherapy/test-of-cure, and to ensure that relapses occurring later would be included in the per protocol analysis performed at late posttherapy.

In the studies which compared 5-day to 10-day treatment regimens (studies 3003 and 3007 in AECB, 3002 and 3005 in acute sinusitis, and 3004 and 3008 in tonsillitis/pharyngitis), the test-of-cure assessment was performed at the same posttherapy ascertainment window in both groups. Therefore, the interval between the end of therapy and the posttherapy/test-of-cure or late posttherapy visits was up to 5 days longer for the telithromycin 5-day regimen *vs* comparator, and early relapses in subjects receiving a short duration of active treatment were thus counted as failure at posttherapy/test-of-cure.

Figure 3.1. General study design for Phase III comparative studies



3.5 Study variables

3.5.1 Infection-related signs and symptoms

The investigator assessed the presence or absence of infection-related signs and symptoms specific for each indication at each visit as specified in the protocols. A severity scale was established to allow for more consistent follow-up throughout the study (intensity of signs and symptoms were to be rated as mild, moderate, or severe).

3.5.2 Categorization of clinical outcome

The clinical outcome was assessed by the investigator based on the evolution of clinical signs and symptoms and X-ray findings. The investigator was asked to classify the outcome as cure, failure, or indeterminate based on definitions specified in the protocol. Subjects with residual symptoms requiring subsequent treatment with other antibiotics were classified as "failure." Subjects who were classified as indeterminate were counted as failures in the mITT analysis but excluded form the PPc analyses. Discontinuation of subjects with a resistant causative pathogen isolated at pretherapy/entry was not mandatory; these subjects could be discontinued from study drug at the discretion of the investigators depending on the clinical status or evolution. Susceptibility of

causative pathogens at the investigator's site was based on inhibition zone values obtained by the disk diffusion method at local laboratories during the study.

3.5.3 Bacteriological evaluation

A sample for bacteriological diagnosis was taken before the treatment where possible in all studies. It may not have been possible to always obtain an adequate specimen for bacteriologic culture because some subjects were unable to produce adequate sputum or either the investigator and/or the subject may not agree to perform procedures such as sinus punctures. In CAP and AECB studies, sputum cultures and blood cultures were performed where possible. Respiratory secretion smears were analyzed by direct microscopy and Gram stain. Gram-stained smears were to be examined for the presence of bacteria, squamous epithelial cells, and polymorphonuclear cells.

In the acute sinusitis studies, sinus puncture cultures were performed on all subjects in Study 3002 at pretherapy/entry, for subjects at selected centers in Study 3005, and for subjects at US sites in Study 3011. In Studies 3002 and 3011, a quantitative culture of the sinus aspiration samples was performed when possible for *Staphylococcus aureus*. This pathogen was considered causative only if the bacterial count was $>10^4$ colony forming units per milliliter (cfu/mL) or classified as "+++" using semi-quantitative methods. In the tonsillitis/pharyngitis studies, throat swab specimens were obtained for a rapid streptococcal antigen test to determine subject eligibility for inclusion and to perform a bacteriological culture. Streptococcal A antigen was detected using test kits (⟶ Kit). In the comparative studies, discontinuation could result from isolation of a pathogen resistant to either telithromycin or the comparator drug. Treatment was also considered a failure if subjects discontinued study medication due to an adverse event and the investigator decided that the anti-infective treatment should be continued with a subsequent antibiotic.

3.5.4 Categorization of bacteriological outcome

Bacteriological response by causative pathogen was categorized at posttherapy/TOC, as defined below:

- Eradication: the causative pathogen was absent.
- Presumed eradication (except in tonsillitis/pharyngitis): the subject had improved clinically to such an extent that a proper follow-up culture could not be obtained.
- Persistence: the causative pathogen was still present whether or not signs of infection were still present.
- Presumed persistence: a subsequent antimicrobial was started before a posttherapy/TOC culture was obtained.
- Recurrence: reappearance of the causative pretherapy/entry pathogen after eradication from the original site of infection.

When new pathogens were isolated, culture results were classified as follows:

- Colonization (eradication with colonization): a new pathogen emerged between the first day of study drug administration and the posttherapy/TOC visit in a subject free of new symptoms.
- Superinfection: a new pathogen emerged during therapy (from the second day of treatment) or within 3 days after treatment had been completed, either at the site of infection or at a distant site with the emergence or worsening of associated clinical or laboratory evidence of infection, and a new systemic anti-infective treatment was prescribed.
- Eradication and reinfection (designated "reinfection" in the clinical study reports): elimination of the initial infecting organism followed by replacement with a new species or

with a new serotype or biotype of the same organism at the same site in the presence of signs and symptoms of infection after completion of therapy.

Bacteriological response by subject was assessed at posttherapy/TOC as satisfactory (eradication, eradication with colonization, presumed eradication) or unsatisfactory (all other categories) based on the by-pathogen bacteriological response at posttherapy/TOC and the presence of new pathogens.

3.6 Definition of equivalence

The two treatments were considered equivalent if the lower limit of the confidence interval was greater than or equal to –15% and the upper limit contained zero, for efficacy rates of 80% to 90%, for the better of the two study drugs. A lower limit greater than or equal to –10% would have been required if the efficacy rate was ≥ 90%. The sample size of each comparative trial was increased to account for the evaluability rate.

The concept of a variable delta for determining equivalence based upon the observed cure rates has been phased out at the agency. A delta which reflects statistical and clinical considerations specific to the disease under consideration is more appropriate. For this review a lower bound of –10% is used as the non-inferiority margin for declaring therapeutic equivalence of telithromycin to comparator. Merely achieving statistical equivalence does not guarantee a win for any drug. While this is generally a necessary condition it is not of itself a sufficient one for approval.

4 COMMUNITY-ACQUIRED PNEUMONIA (CAP)

In support of the claim for CAP Aventis Pharmaceuticals, Inc. presented data from 3 double-blind, randomized, active-controlled trials (3001, 3006, 3009) and 3 open label trials (3000, 3009OL, 3010). Study 3009 was designed as an adequately powered comparative trial which had its comparator arm terminated before the end of the trial because trovafloxacin (the comparator), had major restrictions placed on its use by the agency and was no longer appropriate for the trial. The study was continued as an open label trial and is presented here as study 3009OL. Essentially, the CAP database consisted of 2 adequate, randomized, double blind, active-comparator trials (studies 3001 and 3006) and 4 supportive trials (3000, 3009, 3009OL, 3010) as shown in Table 4.1.

Table 4.1. Phase III clinical studies to demonstrate the efficacy and safety of telithromycin for the treatment of subjects with community acquired pneumonia

Indication / Study number (region)	Design	Treatment Regimen: Telithromycin 800 mg	Treatment Regimen: Comparator
3000 (Europe)	Open label	7–10 d	NONE
3001 (Europe)	Double blind, randomized, active comparative, 2-arm, parallel group	10 d	Amoxicillin 1000 mg PO tid x 10 d
3006 (US+)[1]	Double blind, randomized, active comparative, 2-arm, parallel group	10 d	Clarithromycin 500 mg tid PO x 10 d
3009 (US+)	Double blind, randomized, active comparative, 2-arm, parallel group	7-10 d	Trovofloxacin 200 mg QD PO x 7-10 d
3009OL(US+)	Open label	7-10 d	NONE
3010 (US+)	Open label	7 d	NONE

4.1 Primary hypotheses

The primary hypotheses across all CAP studies were to demonstrate equivalence of 800 mg oral telithromycin once a day for 7-10-days and comparator with respect to clinical efficacy and bacteriologic efficacy the TOC visit in the PPc and mITT populations. The open label studies aimed to demonstrate the clinical efficacy in a specific study population. The modified intent-to-treat (mITT) population was expected to demonstrate evidence of efficacy that supports the conclusions from the PPc populations.

4.2 Secondary hypotheses

The secondary hypotheses were to evaluate the bacteriological efficacy of telithromycin in the specified population based on the protocol at the TOC visit with specific interest in the main pathogens suspected as the causative agent for CAP in the bacteriologic per protocol (PPb) and the bacteriologic mITT (bmITT) populations. Additionally, there is specific interest in the efficacy of telithromycin in the treatment of subjects with CAP who had a *S. pneumoniae* pathogen which was resistant to penicillin G and/or erythromycin A.

The design and conduct of these trials were submitted for FDA review. The target population was subjects with mild to moderate CAP infection who could be treated in an outpatient setting. The open label trials utilized similar protocols for enrollment and monitoring. The clinical reviewer agreed with sponsor's evaluability criteria and accepted the sponsors data.

4.3 Inclusion/exclusion

Adult male and female (age > 18 years) were enrolled if they met the inclusion/exclusion criteria to satisfy a clinical and radiologic diagnosis of CAP. Measures were taken to ensure that the subjects included in this trial who were representative of the population with CAP. The population studies consisted of subjects with mild to moderate infection. Subjects with concomitant RTIs were excluded.

4.5 Prior and concomitant treatments

All additional treatments being taken on entry to the study or at any time during the study were regarded as concomitant treatments. No oral or parenteral concomitant antimicrobial treatments were permitted for the duration of study medication. Subjects who required such antimicrobial treatments other than the study medication during the study were to be discontinued from study medication.

In the mITT population, the mean duration of treatment with telithromycin in the CAP studies was 8.7 days (median 10.0, ranging from 1 to 15 days) for all CAP studies. The mean number of doses of active treatment was 8.5 (median 10.0, ranging from 0 to 10 doses). In Study 3010 the treatment duration was limited to 7 days. Hence in all CAP studies (mITT population), 449 subjects were treated for 7 days, compared with 26 subjects treated for 8 days, 29 subjects for 9 days, 598 subjects for 10 days, 153 subjects for 11 days, and 23 subjects for >11 days. Duration of therapy was similar for comparators.

4.6 Demographics characteristics

The distribution of demographic factors was similar across treatment regimens in the mITT population is shown in Table 4.2. The treatment groups were also balanced within individual protocols for the mITT, PPc, bmITT and PPb populations. The treatment groups were balanced with respect to age, sex, race and smoking status for all comparative studies. Demographic characteristics were similar for the open label studies. The within study distribution of baseline characteristics were similar and produced no notable departures from the information displayed in table 4.6 for the pooled population.

Table 4.2. CAP: Key demographic characteristics for subjects in the mITT population

Characteristic	All comparative studies		All CAP studies	
	Telithromycin	Comparators	Telithromycin	Comparators
Total Treated	503	521	1373	521
Sex				
Male	266 (52.9)	263 (50.5)	779 (56.7)	263 (50.5)
Female	237 (47.1)	258 (49.5)	594 (43.3)	258 (49.5)
Age				
Mean (years)	44.8	45.5	44.6	45.5
13 to 18 years	13 (2.6)	18 (3.5)	34 (2.5)	18 (3.5)
>18 to <65 years	407 (80.9)	416 (79.8)	1143 (83.2)	416 (79.8)
>65 years	83 (16.5)	87 (16.7)	196 (14.3)	87 (16.7)
Race				
White	408 (81.1)	422 (81.0)	986 (71.8)	422 (81.0)
Black	75 (14.9)	76 (14.6)	286 (20.8)	76 (14.6)
Asian	3 (0.6)	5 (1.0)	23 (1.7)	5 (1.0)
Other	17 (3.4)	18 (3.5)	78 (5.7)	18 (3.5)
Smoker	164 (32.6)	209 (40.1)	475 (34.6)	209 (40.1)

For CAP the pre-entry characteristics in the mITT population were balanced for telithromycin and comparators. The population captured about 4% bacteremic patients (blood cultures were obtained at entry) and the subjects largely represented mild to moderate CAP as evidenced by the majority of fine category I or II (telithromycin: 84%, comparators: 79.8%) as shown in Table 4.3.

Table 4.3. CAP: Key pretherapy/entry characteristics in the mITT population

	All CAP Studies			
	Telithromycin		Comparators	
Characteristic	N	(%)	N	(%)
Total Treated	1373	(100)	521	(100)
At least 1 risk factor for morbidity [a]	410	(29.9)	176	(33.8)
Fever >39°C	626	(45.6)	230	(44.1)
WBC >10^3/mm^3	658	(47.9)	248	(47.6)
Documented pneumococcal bacteremia	56	(4.1)	18	(3.5)
Severity, moderate [b]	954	(69.5)	378	(72.6)
Fine score				
Class I	685	(49.9)	244	(46.8)
Class II	468	(34.1)	172	(33.0)
Class ≥III	220	(16.0)	105	(20.2)

[a] COPD, asthma, interstitial lung disease, respiratory insufficiency, congestive heart failure, coronary artery disease, atrial fibrillation, cerebrovascular disease, diabetes mellitus, renal disease, liver, disease, cancer/neoplastic disease.
[b] As assessed by the investigator.

4.7 Clinical response

The primary efficacy analysis in CAP was the analysis of clinical outcome at posttherapy/TOC in the per protocol population of subjects (PPc). Similar analyses are performed for the mITT populations and the mITT populations are expected to demonstrate similar conclusions to the results from the PPc population. Clinical response at the TOC visit are summarized in Table 4.4.

Table 4.4. CAP: Clinical cure rates by study for telithromycin and comparator(s) at the posttherapy/TOC visit

		Telithromycin			Comparator			95% C.I.[a]
Protocol No.		N	n	(%)	N	n	(%)	(%)
PPc								
	3001	149	141	(94.6)	152	137	(90.1)	(-2.1; 11.1)
	3006	162	143	(88.3)	156	138	(88.5)	(-7.9; 7.5)
	3009	80	72	(90.0)	86	81	(94.2)	(-13.6; 5.2)
	3000	197	183	(92.9)				
	3009OL	187	175	(93.6)				
	3010	357	332	(93.0)				
mITT								
	3001	199	171	(85.9)	205	161	(78.5)	(-0.5; 15.3)
	3006	204	161	(78.9)	212	171	(80.7)	(-9.9; 6.5)
	3009	100	82	(82.0)	104	89	(85.6)	(-14.7; 7.5)
	3000	240	191	(79.60				
	3009OL	212	182	(85.8)				
	3010	418	357	(85.4)				

[a] 95% confidence interval of the difference in cure rates between the treatment groups.

The two comparative studies at posttherapy/TOC in the PPc population were completed with the planned number of subjects (Study 3001 *vs* amoxicillin; Study 3006 *vs* clarithromycin). Studies 3001 and 3006 had clinical cure rates for telithromycin 94.6% (amoxicillin [90.1%]) and 88.3% (clarithromycin [88.5%]), respectively. In both studies the clinical cure rates for the 10-day telithromycin treatment and the 10-day comparator treatment achieved a lower bound for declaring therapeutic equivalence of ≥-10%. One may conclude that in the PPc and mITT populations for studies 3001 and 3006 the clinical cure rates for telithromycin were no worse than those of the respective comparators. Study 3009 was stopped prematurely before the planned sample size was reached. The clinical cure rates in this study is comparable to that observed in the other 2 comparative studies, the confidence interval is wider, and the lower bound lies just inside

the –15% boundary. Clinical cure rates in the mITT populations were lower than those in the PPc populations because subjects with indeterminate responses (such as missing information for assessment of clinical status) were counted as failures in the mITT analysis.

4.8 Bacteriological outcome by subject

The bacteriological outcome was similar between telithromycin and active comparators for the PPb and bmITT populations, as shown in Table 4.5. The bacteriologic eradication rates were similar for telithromycin and comparators in the PPb and bmITT populations. The rates observed in the open label studies were similar to those seen in the active-controlled studies.

Table 4.5. CAP: Subjects with satisfactory [a] bacteriological outcome at the posttherapy/TOC visit in the PPb and bmITT populations

	Telithromycin			Comparator		
Protocol	**N**	**n**	**(%)**	**N**	**n**	**(%)**
PPb						
3001	40	36	(90.0)	40	35	(87.5)
3006	28	25	(89.3)	28	27	(96.4)
3009	14	13	(92.9)	22	22	(100.0)
3000	45	40	(88.9)			
3009OL	68	61	(89.7)			
3010	149	137	(91.9)			
bmITT						
3001	56	49	(87.5)	54	46	(85.2)
3006	40	36	(90.0)	39	37	(94.9)
3009	29	27	(93.1)	32	30	(93.8)
3000	54	49	(90.7)			
3009OL	88	80	(90.9)			
3010	239	215	(90.0)			

[a] Satisfactory = eradication, eradication with colonization, or presumed eradication

4.9 Bacteriological eradication and clinical cure rate by pathogen

The bacteriological eradication rate (documented and presumed eradication) and clinical cure rate at posttherapy/TOC for the PPb population (pooled across all studies) are presented in Table 4.6 for the common causative pathogens for CAP. The overall eradication rate was 90.5% regardless of pathogen. The highest clinical cure rate was observed in subjects with *S. pneumoniae* isolates. The cure rates for pathogens of interest in respiratory tract infections were similar for telithromycin and comparators.

Table 4.6. CAP: Bacteriological eradication and clinical cure rates by pathogen in telithromycin-treated subjects in the PPb population

Causative pathogen	Bacteriological eradication			Clinical cure		
	N	n	(%)	N	n	(%)
S. pneumoniae	174	166	(95.4)	174	165	(94.8)
H. influenzae	105	94	(89.5)	105	95	(90.5)
M. catarrhalis	30	27	(90.0)	30	26	(86.7)
S. aureus	19	15	(78.9)	19	15	(78.9)
Other	114	98	(86.0)	114	102	(89.5)
Total (all pathogens)	442	400	(90.5)	442	403	(91.2)

For penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 13/16 (81.3%) isolates as shown in Table 4.7. For erythromycin A-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was also cure in 13/16 (81.3%) isolates.

Table 4.7. CAP: Clinical cure rates at posttherapy/TOC for resistant S. pneumoniae isolates [a] from single and mixed pathogen infections in telithromycin-treated patients in the PPb population pooled across all studies

	All Studies		
Causative pathogen	N	n	(%)
All *S. pneumoniae*	174	165	(94.8)
Pen-R	16	13	(81.3)
Ery-R	16	13	(81.3)
Pen-R or Ery-R	23	20	(87.0)

Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC 1.0 ≥ µg/mL).

4.10 S. pneumoniae isolated by blood culture

Clinical cure rates for *S. pneumoniae* infections in telithromycin-treated subjects, including infections due to resistant pathogens, isolated from blood cultures are summarized in Table 4.8 for single and mixed pathogen infections. The clinical cure rate in subjects with pneumococcal bacteremia was 38/40 (95.0%) of subjects with single pathogen infections cured, and 43/47 (91.5%) of subjects with mixed pathogen infections. While the cure rates are adequate, these represent limited data from which to draw meaningful conclusions.

Table 4.8. CAP: Clinical cure rates for single and mixed S. pneumoniae isolated from blood cultures in telithromycin-treated subjects at posttherapy/TOC – PPb population

	Single infections		Mixed infections		Single and mixed infections	
Causative pathogen	N	n	N	n	N	n
All *S. pneumoniae*	40	38	7	5	47	43
Pen-R	5	4	1	0	6	4
Ery-R	3	2	3	2	6	4
Pen-R or Ery-R	6	5	3	2	9	7

Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = Erythromycin A-resistant (MIC ≥1.0 µg/mL).

Table 4.9 displays clinical cure rates for subjects with atypical pathogens. These represent sparse data from which to draw any conclusions although the clinical cure rates appear acceptable.

Table 4.9. CAP: Clinical outcome at posttherapy/TOC in atypical pathogen isolates in the PPc population using highly specific criteria determined by the FDA

Pathogen	Telithromycin			Comparator	
	N	n	(%)	N	n (%)
Chlamydia pneumoniae	34	32	(94.1)	18	17 (94.4)
Mycoplasma pneumoniae	31	30	(96.8)	19	18 (94.7)
Legionella pneumophila	12	12	(100.0)	3	2 (66.7)

Table 4.10 shows clinical cure rates for telithromycin in the treatment of subjects who were at increased risk of morbidity and mortality. Clinical outcome was comparable in subjects >65 years (clinical cure = 90.3%) with those <65 years of age (clinical cure = 92.7%). Among subjects with bacteremia the clinical success rate was 91.5% (43/47). In subjects with more severe disease (Fine score ≥III) the clinical cure rate was also >92.0% (161/175).

Table 4.10. CAP: Clinical cure rate in subgroups of special interest in telithromycin-treated subjects at posttherapy/TOC in the PPc population across all studies

Subgroup	Clinical cure N	n	(%)
Per protocol (overall)	1132	1046	(92.4)
Age (years)			
<65	978	907	(92.7)
>65	154	139	(90.3)
Pneumococcal bacteremia [a]	47	43	(91.5)
Fine score			
Class I	554	517	(93.3)
Class II	403	368	(91.3)
Class >III	175	161	(92.0)

4.11 Overall conclusions on the efficacy of telithromycin for CAP

There were 6 phase III clinical trials conducted for the CAP indication: 3 comparative (protocols 3001, 3006 and 3009) and 3 open label (protocols 3000, 3009OL and 3010). All studies used a dose of 800 mg oral telithromycin daily for dosing regimens of 7 to 10 days.

Telithromycin 800 mg was administered to 1373 subjects with CAP. Telithromycin given orally at 800 mg once daily for 10 days was equivalent in clinical efficacy at posttherapy/TOC to clarithromycin given orally at 500 mg bid for 10 days (Study 3006) and amoxicillin given orally 1000 mg tid for 10 days (Study 3001) in the treatment of adult subjects with CAP. In Study 3009, clinical cure rates were >90% for both telithromycin (800 mg orally once a day for 7-10 days) and trovafloxacin (200 mg orally once daily for 7-10 days). In all studies, results in the mITT populations were consistent with the results observed in the PPc population.

Telithromycin showed similar efficacy in subgroups of interest with cure rates of over 90% in study subjects with an increased risk of morbidity, such as subjects >65 years of age, Fine score ≥III, and subjects with documented pneumococcal bacteremia (43/47 subjects), and diagnosis of atypical pathogens: *Legionella pneumophila* 100% (12/12 subjects), *Mycoplasma pneumoniae* 96.8% (30/31 subjects), and *Chlamydia pneumonia* 94.1% (32/34 subjects). While the bacteriologic activity of telithromycin against the pathogens of interest for empiric therapy in treating upper respiratory infections appears to show efficacy these are sparse data except for the penicillin G. sensitive *S. pneumoniae*. Overall, the body of bacteriologic evidence on which the grant a claim for resistant pathogens is minimal.

5 ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB)

The clinical and bacteriological effectiveness of 800 mg telithromycin administered once daily for 5 days in the treatment of acute exacerbation of chronic bronchitis (AECB) in adults was evaluated in two international/multi-center, randomized, double-blind, active-comparator comparative studies as shown in Table 5.1. Study 3003 focused on clinical efficacy in subjects with documented associated chronic obstructive pulmonary disease (COPD) and used amoxicillin/clavulanic acid at 500/125 mg tid as the comparator. Study 3007 was aimed to provide clinical and bacteriological efficacy data for a broad population of subjects with AECB and used cefuroxime axetil at 500 mg bid as the comparator. Both active comparators were chosen because of their *in vitro* activity against the main pathogens associated with AECB (*H. influenzae, S. pneumoniae*, and *M. catarrhalis*).

Table 5.1. AECB: Studies conducted

Protocol No.	Treatment regimen			No. in mITT
3003	TEL	5 d	800 mg qd	160
	AMC	10 d	500 mg/125 mg tid	160
3007	TEL	5 d	800 mg qd	182
	CXM	10 d	500 mg bid	191

TEL = telithromycin, AMC = amoxicillin/clavulanic acid (Augmentin®), CXM = cefuroxime axetil

Pretherapy/entry characteristics, including smoking status, clinical findings, characteristics of the current AECB episode, and medical history, were generally similar among subjects who received telithromycin or comparator within each study and for the pooled analysis across the mITT, PPc, and PPb populations. However, Study 3003, performed in subjects with associated COPD, enrolled more subjects with a higher risk of morbidity (subjects >65 years old, FEV_1/FVC <60%) than Study 3007. The subject disposition is shown in Table 5.2.

Table 5.2. AECB: Subject disposition

Population	Telithromycin	Comparators	Total
Randomized	346	354	700
Treated	343	352	695
mITT	342	351	693
PPc	255	254	509
bmITT	82	79	161
PPb	64	58	122

5.1 Demographic characteristics

Demographic characteristics of the telithromycin treated patients in the AECB trials were similar to those of the comparators or each study as well as the pooled population. The trials enrolled similar patients for both studies, however, Study 3003 enrolled a higher number of patients with a known history of COPD (98% vs 50%) and subjects who had FEV_1/FVC <60% (within the previous 12 months prior to entry into the study (43% vs 7%). In the mITT population, the mean duration of treatment with telithromycin was 4.9 days (median 5.0, range: 1 to 5 days) for all AECB studies and was approximately 10 day for comparators. Compliance with treatment was similar for telithromycin and comparators.

5.2 Prior and co-intervention measures

All additional treatments being taken on entry to the study or at any time during the study were documented as concomitant treatments. Subjects who required oral or parenteral antimicrobial treatments other than the study medication during the study were to be withdrawn from study medication. If concomitant non-antimicrobial treatments were considered to be necessary for the subject's welfare and were unlikely to interfere with the study medication, they could be given at the discretion of the investigator. Concomitant bronchodilator therapy was allowed in those subjects who were currently receiving such therapy at study entry, or at any time during the course of therapy, in subjects where the investigator it to be warranted.

5.3 Efficacy ascertainment

The primary efficacy data were clinical outcome at the posttherapy/TOC visit. The clinical outcome was assessed by the investigator using the following criteria from the pretherapy/entry visit to the TOC: infection-related signs and symptoms of AECB (graded using an absent, mild, moderate), severity rating (0-3) scale, and peak expiratory flow rates. Investigators were asked to classify the clinical outcome of the subject as either cure, failure or indeterminate as defined in the protocol. If the investigator determined that any residual symptoms required subsequent

antibiotics those patients were classified as failures. Secondary efficacy data were bacteriological outcome at TOCV and at late posttherapy visits.

5.4 Interim analysis

Study 3003: According to Sponsor clinical study report:

> "After completion of 50% of the planned sample size (170 subjects), a one-sided chi square test at the 5% level for the difference in cure rates between the two treatment groups was performed in the PPc population. The study was to be stopped if the telithromycin 5-day treatment group was significantly inferior to the amoxicillin/ clavulanic acid treatment group. There was no adjustment of the type I error rate in the final analysis because this interim analysis was for safety reasons alone: in particular, it was not possible to stop the trial at the interim analysis and declare equivalence."

Sponsor's description of the interim analysis procedure indicates that the trial could be stopped based on one group being significantly inferior to the other. This is interpreted to mean it could be stopped due to efficacy or lack of efficacy. Despite the fact that the trial was not stopped the confidence interval should be adjusted to account for the interim look (type I error rate of 0.025).

5.5 Clinical outcome

The primary efficacy analyses in AECB were the analyses of clinical outcome at posttherapy/TOC (Days 17-21) in the PPc and mITT populations. Clinical outcome at posttherapy/TOC for the PPc and mITT populations are summarized in Table 5.3. Table 5.3 displays both confidence intervals for Study 3003 and the both analyses led to the same conclusion.

Table 5.3. AECB: Clinical cure rate by study for telithromycin and comparator(s) at posttherapy/TOC

	Telithromycin			Comparator			95% C.I.
Protocol No.	N	n	(%)	N	n	(%)	
PPc							
3003	115	99	(86.1)	112	92	(82.1)	(-6.4; 14.3) (-7.8, 15.7)[a]
3007	140	121	(86.4)	142	118	(83.1)	(-5.8; 12.4)
mITT							
3003	160	130	(81.3)	160	125	(78.1)	(-6.3; 12.6) (-6.9, 13.6)[a]
3007	182	142	(78.0)	191	138	(72.3)	(-3.5; 15.1)

[a] The 97.5% C.I. –adjusted for one interim look at the data.

The clinical outcome at posttherapy/TOC in the PPc population indicates the 5-day telithromycin was not therapeutically inferior to the 10-day amoxicillin/clavulanic acid treatment or to the 10-day cefuroxime axetil treatment in the treated PPc and mITT populations. Clinical outcome evaluated at the late posttherapy visit was a secondary efficacy variable and is summarized in Table 5.4. In both studies the analysis of clinical outcome at the late posttherapy supports the conclusion of the primary analysis by demonstrating that telithromycin was not inferior to the comparators in the mITT and PPc populations.

Table 5.4. AECB: Clinical cure rate by study for telithromycin and comparator(s) at LPTV

		Telithromycin			Comparator			95% CI
Protocol No.		N	n	(%)	N	n	(%)	
PPc								
	3003	105	82	(78.1)	108	81	(75.0)	(-9.2;15.4)
								(-10.8; 17.0)[a]
	3007	131	103	(78.6)	136	104	(76.5)	(-8.6; 12.9)
mITT								
	3003	160	118	(73.8)	160	114	(71.3)	(-7.9;12.9)
								(-9.3; 14.3)[a]
	3007	182	125	(68.7)	191	124	(64.9)	(-6.3; 13.8)

[a] The 97.5% C.I. –adjusted for one interim look at the data.

Therefore, the shorter duration of treatment with telithromycin was not associated with a higher rate of relapse even though telithromycin was assessed within a window 5 days longer than for the comparators.

5.6 Bacteriological outcome by subject

In Study 3003, satisfactory bacteriological outcome was lower in both the telithromycin group and the amoxicillin/clavulanic acid group than in Study 3007. One possible explanation is that the lower cure rate may be due to the greater severity of disease in Study 3003 in which all subjects had documented bronchial obstruction.

Table 5.5. AECB: Subjects with bacteriological outcome "satisfactory" [a] by study

	Telithromycin			Comparator		
Protocol No	N	n	(%)	N	n	(%)
PPb population						
3003	39	27	(69.2)	30	21	(70.0)
3007	25	19	(76.0)	28	22	(78.6)

[a] Satisfactory = eradication, eradication with colonization, or presumed eradication

5.7 Bacteriological eradication and clinical cure rate by pathogen

Bacteriological eradication and clinical cure rates for select causative pathogens in telithromycin-treated subjects combined across studies are presented in Table 5.6. Telithromycin cure rate for subjects with *H. influenzae*, the most commonly observed pathogen, was 60% (15/25) compared to 88% (15/17) for the comparators.

Table 5.6. AECB: Bacteriological eradication by pathogen in the PPb population combined across both studies

	Telithromycin			Comparators		
Causative pathogen	N	n	(%)	N	n	(%)
S. pneumoniae	14	13	(92.9)	12	9	(75.0)
Pen-R	0			2	1	(50.0)
Ery-R	0			3	2	(66.7)
H. influenzae	25	15	(60.0)	17	15	(88.2)
M. catarrhalis	10	10	(100.0)	16	14	(87.5)
S. aureus	2	2	(100.0)	3	2	(66.7)
Other	19	14	(73.7)	20	13	(65.0)
Total (all pathogens)	70	54	(77.1)	68	53	(77.9)

Pen-R = penicillin G-resistant, Ery-R = erythromycin A-resistant.

5.8 Overall conclusions on the efficacy of telithromycin for AECB

Telithromycin 800 mg once daily for 5 days was shown to be equivalent in clinical efficacy to cefuroxime axetil given for 10 days, and was similar to amoxicillin/clavulanic acid given for 10 days in subjects with AECB of mild to moderate severity. Bacteriological eradication and clinical cure rates by pathogen were satisfactory in telithromycin-treated subjects for *S. pneumoniae 93% (13/14), H. influenzae 60% (15/25),* and *M. catarrhalis* 100% (10/10). These constitute very few pathogens from which to conclude bacteriological efficacy although telithromycin appears to show some efficacy with respect to the main pathogens of interest except for *H. influenzae* in subjects with AECB.

6 Acute sinusitis

The clinical and bacteriological effectiveness of 800 mg oral telithromycin administered once daily for 5 or 10 days in the treatment of acute sinusitis in adults was evaluated in three international/multicenter, randomized, double-blind, comparative studies (Studies 3002, 3005, and 3011).

Study 3002 was to investigate the clinical efficacy and bacteriological eradication rate of telithromycin 800 mg qd for 5 days *vs* telithromycin 800 mg qd for 10 days in subjects with pathogens isolated at pretherapy/entry by sinus puncture in selected study sites. All subjects had sinus puncture at entry, and sinus X-ray findings were to show either total opacity or air fluid levels in all subjects.

Study 3005 was an active-comparator, three-arm study comparing the efficacy and safety of oral telithromycin 800 mg qd for 5 days *vs* oral telithromycin 800 mg qd for 10 days *vs* oral amoxicillin/clavulanic acid 500/125 mg administered tid for 10 days. The 5 day telithromycin regimen was to be compared with amoxicillin/clavulanic acid only if the 10 day regimen showed statistical equivalence. Sponsor used a –15% lower bound of the confidence interval to determine therapeutic equivalence which is based on the former agency rule. Given that the agency is in transition regarding non-inferiority determination we used sponsor's lower bound for this particular situation. In this situation there was no need to further adjust for multiplicity since the 5 day telithromycin group was compared in a sequential fashion.

Study 3011 was a double-blind study comparing 5 days of telithromycin treatment (800 mg qd) with 10 days of cefuroxime axetil (250 mg bid) using a 2:1 randomization scheme (telithromycin :cefuroxime axetil). Bacterial documentation was obtained by sinus puncture at the US sites and by sinus endoscopy at non-US sites.

Table 6.1. Acute sinusitis studies

Protocol No.	Treatment regimen			No. in mITT
3002	TEL	5 d	800 mg qd	167
	TEL	10 d	800 mg qd	168
3005	TEL	5 d	800 mg qd	201
	TEL	10 d	800 mg qd	204
	AMC	10 d	500/125 mg tid	202
3011	TEL	5 d	800 mg qd	240
	CXM	10 d	250 mg bid	116

TEL = telithromycin; AMC = amoxicillin/clavulanic acid (Augmentin®); CXM = cefuroxime axetil

The subject disposition is shown in Table 6.2.

Table 6.2. Acute sinusitis: Subject disposition by duration of treatment

Population	Telithromycin 5-day	Telithromycin 10-day	Comparator 10-day	Total
Randomized	667	428	374	1469
Treated	665	425	373	1463
mITT population	608	372	318	1298
PPc population	458	273	226	957
bmITT population	232	113	71	416
PPb population	177	76	57	310

There were 13 adolescent subjects treated with telithromycin. The distribution of demographic characteristics was similar for telithromycin and comparators as shown in Table 6.3. The distribution of these characteristics shown below was similar for each study taken individually.

Table 6.3. Acute sinusitis: Key demographic characteristics for telithromycin-treated subjects in the mITT population across all three studies

Subgroup	Telithromycin 5-day		Comparators 10-day	
Total	608	(100)	372	(100)
Sex				
Male	275	(45.2)	167	(44.9)
Female	333	(54.8)	205	(55.1)
Age (yrs)				
Mean	39.2		40.3	
13 to 18	13	(2.1)	4	(1.1)
>18 to <65	563	(92.6)	352	(94.6)
>65	32	(5.3)	16	(4.3)
Race				
White	556	(91.4)	349	(93.8)
Black	24	(3.9)	13	(3.5)
Asian/Oriental	20	(3.3)	7	(1.9)
Other	8	(1.3)	3	(0.8)

Key pre-entry characteristics are shown in Table 6.4. In Study 3002, all the subjects had total opacity or air fluid level findings on X-ray. Compared with Studies 3005 and 3011, fewer telithromycin subjects in Study 3002 had prior episodes of allergic rhinitis in the last 30 days, a history of asthma, or prior ENT-related surgery.

Table 6.4. Acute sinusitis: Key pretherapy/entry characteristics of telithromycin-treated subjects – mITT population

Subgroup	Telithromycin 5 days		Telithromycin 10 days		Comparators 10 days	
Total	608		372		318	
Sinus puncture at entry	325	(53.5)	188	(50.5)	78	(24.5)
Sinus x-ray findings						
Total opacity	235	(38.7)	136	(36.6)	64	(20.1)
Air fluid level	252	(41.4)	157	(42.2)	139	(43.7)
Mucosal thickening only [a]	166	(27.3)	97	(26.1)	130	(40.9)
Prior episode of allergic rhinitis in the past 30 days	93	(15.3)	25	(6.7)	56	(17.6)
History of asthma	72	(11.8)	36	(9.7)	42	(13.2)
Prior ENT-related surgery	118	(19.4)	48	(12.9)	55	(17.3)

[a] Level of mucosal thickening in Study 3005 was ≥6 mm. The level in Study 3011 was ≥10 mm. Only total opacity or air fluid level were to be present in Study 3002.

6.1 Clinical outcome

The primary efficacy analysis in acute sinusitis was the analysis of clinical outcome at posttherapy/TOC (Days 17-24) in the PPc and mITT populations. Clinical outcome at posttherapy/TOC is summarized in Table 6.5.

Table 6.5. Acute sinusitis: Clinical cure rate by study at posttherapy/TOC

	Telithromycin						Comparators			95% C.I.
	5 days			10 days			10 days			
Protocol No.	N	n	(%)	N	n	(%)	N	n	(%)	
PPc										
3002	123	112	(91.1)	133	121	(91.0)	N/A			(-7.7; 7.9)
3005	146	110	(75.3)				137	102	(74.5)	(-9.9; 11.7)
3005				140	102	(72.9)	137	102	(74.5)	(-12.7; 9.5)
3011	189	161	(85.2)	NA			89	73	(82.0)	(-7.1; 13.4)
mITT										
3002	167	138	(82.6)	168	147	(87.5)	N/A			(-13.1; 3.3)
3005	201	140	(69.7)				202	138	(68.3)	(-8.2; 10.9)
3005				204	140	(68.6)	202	138	(68.3)	(-9.2; 9.8)
3011	240	193	(80.4)	NA			116	84	(72.4)	(-2.2; 18.2)

Comparators = amoxicillin/clavulanic acid (Study 3005); cefuroxime axetil (Study 3011). N/A = not applicable.

The efficacy results at the posttherapy/TOC for Study 3002 (which did not have a non-telithromycin arm) showed a 91% cure rate with a 95% C.I. of (-7.7%, 7.9%) for telithromycin 5-d and telithromycin 10-d treatments in the PPc population. However, in the mITT population the 5-d group had about a 7% reduction in clinical efficacy compared to about 4% for the 10-d group (telithromycin 5-d: 82.6%, telithromycin 10-d: 87.5%; with a 95% C.I. of [-13.1%, 3.3%]). In Study 3005 the clinical cure rates were about 16% to 18% lower than those observed in study 3002 for both the telithromycin 5-d (75.3% vs 91.1%) and telithromycin 10-d (72.9% vs 91%) regimens although similar to amoxicillin/clavulanic acid. The 95% C.I. for the difference in cure rate for telithromycin 5-d compared to amoxicillin was in the PPc population was (-12.7% ; 9.5%) and (-9.2%; 9.8%) in the mITT population. In study 3011 the clinical cure rates were (telithromycin 5-d: 85.2%; cefuroxime axetil: 82.0%; with a 95% C.I. of [–7.1%; 13.4%]) in the PPc population and were (telithromycin 5-d: 80.4%; cefuroxime axetil: 72.4%; with a 95% C.I. of [–2.2%; 18.2%]) in the mITT population.

The efficacy results at the late posttherapy visit for Study 3002 (which did not have a non-telithromycin arm) showed about 89% cure rate with a 95% C.I. of (-9.3%, 8.7%) for telithromycin 5-d and telithromycin 10-d treatments in the PPc population. In the mITT population the clinical cure rates were (telithromycin 5-d: 80.8%; telithromycin 10-d: 89.3%; with a 95% C.I. of [-14.1%, 3.0%]). While the 10-d telithromycin group appears to sustain it clinical cure rate until the late posttherapy visit, the telithromycin 5-d group had about an 8% reduction. In Study 3005 the clinical cure rates were about 13% to 18% lower than those observed in study 3002 for both the telithromycin 5-d (88.9% vs 69.9%) and telithromycin 10-d (89.2% vs 67.7%) regimens although similar to amoxicillin/clavulanic acid. The 95% C.I. for the difference in cure rate for telithromycin 5-d compared to amoxicillin was in the PPc population was (-12.7% ; 0.8%) and (-9.5%; 10.1%) in the mITT population. In study 3011 the clinical cure rates were (telithromycin 5-d: 79.9%; cefuroxime axetil: 78.0%; with a 95% C.I. of [–9.8%; 13.5%]) in the PPc population and (telithromycin 5-d: 74.2%; cefuroxime axetil: 65.4%; with a 95% C.I. of [–3.1%; 18.7%]) in the mITT population.

Table 6.6. Acute sinusitis: Clinical cure rate by study at the late posttherapy visit

	Telithromycin						Comparators			95% CI
	5 days			10 days			10 days			
Protocol No.	N	n	(%)	N	n	(%)	N	n	(%)	
PPc										
3002	108	96	(88.9)	120	107	(89.2)	N/A			(-9.3; 8.7)
3005	136	95	(69.9)				130	92	(70.8)	(-12.7; 0.8)
3005				133	90	(67.7)	130	92	(70.8)	(-15.0; 8.8)
3011	174	139	(79.9)	N/A			82	64	(78.0)	(-9.8; 13.5)
mITT										
3002	167	135	(80.8)	168	145	(89.3)	N/A			(-14.0; 3.0)
3005	201	132	(65.7)				202	132	(65.3)	(-9.5; 10.1)
3005				204	132	(64.7)	202	132	(65.3)	(-10.4; 9.1)
3011	240	178	(74.2)	N/A			116	77	(65.4)	(-3.1; 18.7)

Comparators = amoxicillin/clavulanic acid (Study 3005); and cefuroxime axetil (Study 3011). N/A = not applicable.

Although Study 3002 was a randomized, double-blind trial it did not have a comparator arm and the potential for bias associated with open label studies cannot be ruled out. Factors which could influence the observed cure rates in this study, such as, underlying allergic disease, season when the study was performed, duration of symptoms at time of entry, and possible viral etiology. Although no clear explanation is apparent at this time one should consider that 62.2% (104/167) presented with signs and symptoms of sinusitis within < 7 days prior to entry into study, during a period when viral etiology is a likely contributor.

In study 3005 the cure rate observed in this study was about 19% lower than that seen in the open label study. Consistent with the number of subjects who presented with < 7 days of signs and symptoms for AMS, this trial had about 40% of the subjects fell into the period when viral etiology is likely. Among subgroups of interest, the clinical cure rate among smokers in the telithromycin 5-d group was about 20% lower than that of non-smokers or ex-smokers (smokers: 57.6%, non-smokers: 77.6%, and ex-smokers 77.4%). This reduction in cure rates among smokers was not seen among subjects treated with amoxicillin/clavulanic acid (smokers: 75.0%, non-smokers: 73.3%, and ex-smokers 78.9%).

6.2 Bacteriological outcome by subject

As shown in Table 6.7, satisfactory bacteriological outcome tended to be higher for telithromycin than for the active comparators.

Table 6.7. Acute sinusitis: Subjects with bacteriological outcome "satisfactory"[a] by study

	Telithromycin						Comparators		
	5 days			10 days			10 days		
Protocol No.	N	n	(%)	N	n	(%)	N	n	(%)
PPb									
3002	70	65	(92.9)	69	62	(89.9)	NA		
3005	7	6	(85.7)	7	6	(85.7)	8	6	(75.0)
3011	100	84	(84.0)	NA			49	39	(79.6)

[a] Satisfactory = cradication, cradication with colonization, or presumed cradication. NA = not applicable.

6.3 Clinical cure rate by pathogen

Clinical cure rates at posttherapy/TOC for selected causative pathogens in the 5-day and 10-day telithromycin treatment groups are presented in Table 6.8 for the PPb population combined across all studies.

Table 6.8. Acute sinusitis: Clinical cure rate by pathogen at posttherapy/TOC in the PPb population combined across all studies

Pathogen	Telithromycin						Comparators		
	5-day			10-day			10-day		
	N	n	(%)	N	n	(%)	N	n	(%)
S. pneumoniae	61	55	(90.2)	30	27	(90.0)	16	14	(87.5)
H. influenzae	48	42	(87.5)	16	15	(93.8)	15	13	(86.7)
M. catarrhalis	14	13	(92.9)	4	3	(75.0)	7	7	(100.0)
S. aureus	19	18	(94.7)	4	4	(100.0)	4	3	(75.0)
Other	81	62	(76.5)	42	38	(90.5)	29	20	(69.0)
Total (all pathogens)[a]	**225**	**192**	**(85.3)**	**99**	**90**	**(90.9)**	**71**	**57**	**(80.3)**

[a] Total pathogens without regard to method of collection of pathogens (i.e., sinus endoscopy, sinus puncture)

Clinical cure rates by pathogen in subjects treated for 5 days with telithromycin and for whom the pathogens were isolated by sinus puncture give similar clinical cure rates (146/177 pathogens, 82.5%) when compared to all sample collection methods combined (192/225, 85.3%). Table 6.9 summarizes the results on resistant *S. pneumoniae*. While the clinical response among subjects with penicillin susceptible S. pneumoniae appears to be about 90%, the clinical response among subjects with either penicillin G and/or erythromycin A resistant S. pneumoniae is about 75% to 83%. However, these estimates are based on extremely sparse data.

Table 6.9. Acute sinusitis: Clinical response subjects with S. pneumoniae resistant isolates[a] from single pathogen infections in telithromycin-treated subjects at posttherapy/TOC in the PPb population across all AMS studies.

	5 days			10 days	
Causative pathogen	**N**	**n**	**(%)**	**N**	**n (%)**
All *S. pneumoniae*	45	40	(88.9)	26	24 (92.3)
Pcn-R	8	6	(75.0)	3	3 (100.0)
Ery-R	10	8	(80.0)	6	5 (83.3)
Pcn-R or Ery-R	12	10	(83.3)	6	5 (83.3)

Pcn-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a]Subjects with *S. pneumoniae* isolates resistant to both penicillin G and erythromycin A are displayed in both subcategories.

The results of the secondary analyses of bacteriological outcome by subject for the PPb population at the posttherapy/TOC visit demonstrated similar bacteriological efficacy for telithromycin and comparators. These are sparse data from which to draw conclusions about bacteriological efficacy for resistant pathogens and may not be adequate to obtain a claim of efficacy of telithromycin for resistant pathogens.

6.4 Overall conclusions on the efficacy of telithromycin for acute sinusitis

Telithromycin 800 mg given orally once daily for 5 days or 10 days were similar in clinical efficacy at posttherapy/TOC (telithromycin 5-d: 91.1%; telithromycin 10-d: 91.0%) in the PPc population (study 3002). In the mITT population the telithromycin 5-day regimen demonstrated approximately 5% lower clinical cure rate compared to the telithromycin 10-day regimen (telithromycin 5-d: 82.6%; telithromycin 10-d: 87.5%). The mITT population did not attain a –10% lower bound of the 95% C.I. for the difference in cure rates (-13.1%; 3.3%). Given that this trial did not include a non-telithromycin comparator arm the cure rates may be subject to the potential biases that may occur in open label studies.

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8 Conclusions on clinical efficacy

In CAP, telithromycin administered orally 800 mg once a day for 7-10 days exhibited efficacy comparable to a broad range of active comparators administered multiple times daily for 10 days (amoxicillin high dosage, 1000 mg three times a day; clarithromycin 500 mg twice a day; trovafloxacin 200 mg once a day). Telithromycin has demonstrated efficacy in the elderly (age >65) and subjects with pneumococcal bacteremia. In addition, acceptable cure rates were obtained in subjects with a diagnosis of penicillin G. sensitive *S. pneumoniae*, which are the infections most frequently associated with morbidity. Telithromycin also demonstrated activity in treating penicillin G and/or erythromycin A resistant *S. pneumoniae* isolates, however, there may not be adequate evidence to support a claim of efficacy in the treatment of resistant *S. pneumoniae*.

In AECB, efficacy with a once daily treatment regimen of 800 mg for 5 days was demonstrated when compared with widely prescribed drugs considered the standard of care (cefuroxime axetil, amoxicillin/clavulanic acid,) given 2 to 3 times daily for 10 days. Efficacy was maintained in patients more likely to require hospitalization, such as the elderly and patients with COPD, (including those with severe obstruction [FEV_1/FVC <60%]).

In acute bacterial sinusitis, efficacy with telithromycin 800 mg once daily for 5 days was demonstrated against cefuroxime axetil and amoxicillin/clavulanic acid given 2 to 3 times daily for 10 days. In this indication two studies also demonstrated that 5 and 10 days of treatment with telithromycin were comparable in the treatment of subjects with S. pneumoniae resistant to erythromycin A and/or penicillin G. In addition, a 5-day regimen has the advantage of reducing the likelihood of missing doses at the end of a prolonged treatment period, which could promote the selection of resistant pathogens.

In tonsillitis/pharyngitis studies due to GABHS among adults, telithromycin 800 mg given orally once a day for 5 days was not equivalent in clinical and bacteriological efficacy to 10 days of penicillin VK, the standard first line therapy for this indication. It also barely achieved the minimum threshold cure rate expected of first line anti-infective therapies for GABHS tonsillitis/pharyngitis. Telithromycin did show clinical and microbiologic equivalence to 10 days of clarithromycin. Telithromycin was effective in the treatment of tonsillitis/pharyngitis infection due to penicillin sensitive *S. pyogenes*.

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