EXECUTIVE SUMMARY

Recommendations

A. Recommendation on Approvability

The applicant has previously provided substantial evidence of efficacy for telithromycin in the treatment of mild to moderate community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS). This review documents the evidence provided to support claims for treatment of penicillin-resistant and erythromycin-resistant *Streptococcus pneumoniae* (PRSP and ERSP, respectively) within those indications. A labeling claim for CAP due to PRSP is approvable, once sufficient evidence of the safety of telithromycin has been provided. This recommendation is based on: 1) the in vitro data that show the mechanism of action of telithromycin is unaffected by penicillin-resistance in *S. pneumoniae*; 2) the previous finding of efficacy for telithromycin in the treatment of CAP (including penicillin-susceptible strains of *S. pneumoniae*); 3) clinical cure rates for CAP due to PRSP of 84.2% (16/19) in the evaluable population and 67.9% (19/28) in the MITT population; 4) the precedent for approval of other products with this claim; and 5) the benefit of an alternative to quinolone treatment for CAP due to PRSP.

The medical officer does not recommend approval for labeling claims for CAP due to ERSP. This recommendation is based on: 1) the lack of any precedent for approval of this claim; 2) the lack of evidence to support the clinical impact of ERSP, as a distinct entity from PRSP, on morbidity or mortality in CAP; 3) the in vitro data showing that erythromycin (macrolide) resistance in *S. pneumoniae* results in a shift in telithromycin MIC, although the organisms remain susceptible to telithromycin; and 4) the clinical cure rates for CAP due to ERSP of 29/37 (78.4%) in telithromycin-treated patients and 3/5 in clarithromycin-treated patients.

The medical officer does not recommend approval of labeling claims for ABS due to ERSP or PRSP. In this indication, there are no data demonstrating increased likelihood of adverse outcomes due to the presence of drug-resistant *Streptococcus pneumoniae*. The high spontaneous resolution rate for patients with ABS limits the conclusions that can be drawn from the small number of subjects with ABS due to PRSP or MRSP.

B. Recommendation on Phase 4 Studies and Risk Management Steps

There are no recommendations for phase 4 studies from the efficacy review. There are no major deficiencies in the efficacy submission that would be addressed by such studies. It is recommended that the applicant periodically monitor the in vitro susceptibility of clinical isolates of respiratory tract pathogens, particularly *Streptococcus pneumoniae*. However, this is a general recommendation for antibiotics approved for these indications. Risk management steps should be addressed in the safety review of this application.

SUMMARY OF CLINICAL FINDINGS

Brief Overview of Clinical Program

Ketek™ (telithromycin) is a ketolide antibiotic developed by Aventis Pharmaceuticals Inc. Telithromycin is manufactured as 400-mg tablets for oral administration. The original NDA for Ketek™ included studies of four indications, community-acquired pneumonia (CAP), acute bacterial exacerbations of chronic bronchitis (ABECB), acute bacterial sinusitis (ABS), and pharyngitis/tonsillitis (P/T). The applicant received an approvable letter for the first three of these indications. An approvable letter was issued because of concerns about the safety of telithromycin. A non-approval letter was issued for the P/T indication.

The approvable letter requested the submission of specific information to address the safety concerns. The safety information is addressed in other reviews. The safety section that follows lists the reviewers for separate parts of this safety information. The approvable letter also requested additional efficacy information. This review addresses the additional efficacy information for treatment of CAP and ABS due to penicillin-resistant and erythromycin-resistant *Streptococcus pneumoniae* (PRSP and ERSP, respectively). The applicant also provided the results of another study of ABECB.

Efficacy

The applicant provided substantial evidence of the effectiveness of telithromycin for the treatment of CAP, ABS and ABECB in the original NDA application.

ABECB: The approvable letter noted an insufficient number of patients with ABECB due to Haemophilus influenzae and Moraxella catarrhalis in the original application. To address this deficiency, the applicant provided the final study report for an additional study of ABECB in the resubmission. Dr. Alma Davidson's review addresses this study and the ABECB indication.

ABS: The original NDA included three studies of ABS. These studies are described in detail in the background section of the clinical review. In these studies, a total of 29 patients were identified with ABS due to PRSP or ERSP. No new studies of ABS were provided in the resubmission. This review provides an analysis of these cases and discusses the basis for making a separate labeling claim for treatment of PRSP and ERSP in ABS. The reviewer does not recommend granting a separate claim for PRSP and ERSP in the ABS indication.

CAP: The original NDA included six studies of CAP. These studies are described in detail in the background section of the clinical review. A total of 49 patients with CAP due to PRSP or ERSP were identified from these trials and two additional studies of this formulation of Ketek™. Supportive evidence was provided with additional cases of CAP

due to PRSP or ERSP from Japanese studies of a different formulation of telithromycin. In cases of CAP due to PRSP (regardless of erythromycin resistance), the clinical cure rate was 16/19 (84.2%) in the per-protocol group and 19/28 (67.9%) in the MITT population. For cases with ERSP isolates (regardless of penicillin resistance), the clinical cure rate was 25/29 (86.2%) in the per-protocol group and 29/37 (78.4%) in the MITT population. In considering claims for CAP due to PRSP and ERSP, the following factors were considered:

- The mechanism of penicillin resistance in *S. pneumoniae* has no effect on the activity of telithromycin.
- Although structurally related to macrolides like erythromycin, telithromycin retains in vitro activity against *S. pneumoniae* with high-level resistance to erythromycin. However, a small shift in minimum inhibitory concentration for telithromycin is seen when comparing ERSP isolates with erythromycin-susceptible strains of *S. pneumoniae*.
- A claim for CAP due to PRSP has been previously granted by the FDA.
- A claim for CAP due to ERSP has not previously been granted.
- The public health impact of ERSP in CAP has not been demonstrated separately from PRSP. This is due, in part, to the fact that there is a high correlation between the presence of penicillin and erythromycin resistance in *S. pneumoniae*.

Substantial evidence has been provided to support the claim for CAP due to PRSP. Clinical outcomes in patients with CAP due to PRSP were similar to overall rates of effectiveness in CAP. Cases included successful treatment of some patients with PRSP bacteremia, even though telithromycin was given orally. For claims of CAP due to ERSP, the reviewer does not recommend granting a separate claim. In order to support such a claim, the applicant would need to provide evidence of the clinical relevance of ERSP as a distinct entity from PRSP.

The reviewer has also performed a separate analysis of the small number of CAP patients with positive test results for *Legionella pneumophila*. Based on this analysis, it appears likely that the majority of identified cases represent patients with false-positive test results. The studies were designed to enroll outpatients with mild to moderate pneumonia, not the typical presentation for Legionnaire's disease. The reviewer does not recommend including *Legionella pneumophila* in the list of pathogens for the CAP indication.

For other pathogens in CAP, ABS, and ABECB, the applicant should provide additional analyses of clinical outcomes for labeling purposes.

Safety

The safety of Ketek™ (telithromycin) is the subject of two separate clinical reviews. The review by Charles Cooper, M.D. summarizes the safety findings from studies submitted to the NDA and post-marketing adverse events from foreign countries where Ketek™ is approved. The review by George Rochester, Ph.D. summarizes the

safety findings from a large safety trial in the usual care setting. Readers should refer to these reviews for details about the safety findings for Ketek™.

Dosing

The proposed dose is the same for all indications, two tablets (800 mg of telithromycin) taken orally once daily. The duration of treatment for acute exacerbations of chronic bronchitis and acute sinusitis is five days. For community-acquired pneumonia, the duration of treatment is 7-10 days. These dosage recommendations are based on the treatment regimens used in the pivotal studies for these indications.

Special Populations

Because this review focused on analyses of specific pathogens, subset analyses of special populations were not performed. The numbers of patients with PRSP or ERSP in these indications are too few to draw any conclusions of differences by age, gender, or race.

CLINICAL REVIEW

1. Introduction and Background

Ketek™ (telithromycin) is an oral ketolide antibiotic developed by Aventis Pharma, Inc. This product was developed for the treatment of various respiratory tract infections. The original NDA for Ketek was submitted to the FDA on February 28, 2000. The original NDA application included studies of community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis, and tonsillopharyngitis. The applicant also sought labeling claims for penicillin-resistant and macrolide-resistant *Streptococcus pneumoniae*. During the review of this application, safety concerns arose related to potential cardiac, hepatic, and visual toxicity. For efficacy, the submitted studies generally supported efficacy, except in tonsillopharyngitis. The applicant was issued a non-approval letter for this indication. The reader should refer to the clinical review by Mamodikoe Makhene, M.D. for further information. An approvable letter was issued on June 1, 2001 for the other indications. The main focus of the letter was to outline additional information needed to assess the safety of Ketek™, but additional efficacy information was also requested. Specifically, the letter included the following:

"Clinical Studies Targeting Resistant Pathogens

You should conduct a large clinical study of CAP/ABS in order to capture further patients with *S. pneumoniae* isolates resistant to penicillin and/or erythromycin, and beta-lactamase producing strains of *H. influenzae*. Within this large database, monitoring and analysis of adverse event reports, including hepatic, cardiac (QT interval) and visual adverse events, are highly recommended in order to obtain a larger safety database upon which to assess the benefit/risk profile.

- Penicillin-resistant *S. pneumoniae* (PRSP) and erythromycin-resistant *S. pneumoniae* (ERSP): Based on our review of the clinical data submitted in your NDA, we have concluded that insufficient data were provided for the treatment of community-acquired pneumonia (CAP) of mild to moderate severity and acute bacterial sinusitis (ABS) due to PRSP and ERSP.

- Acute Bacterial Sinusitis: Before we would be prepared to approve a PRSP or ERSP claim for ABS, you should establish clinical efficacy of telithromycin against PRSP in a more serious indication (e.g., CAP)."

"General Comments:

- Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB): Your current application regarding *H. influenza[e]* and *M. catarrhalis* is insufficient due to low numbers of isolates."

During subsequent meetings, the applicant proposed a large study to address safety concerns, separate from efforts to collect more patients with PRSP and ERSP. The

applicant would also provide three additional studies of CAP (1 from Japan) and one study of AECB. The applicant completed these studies and submitted them to the FDA in an NDA resubmission on July 27, 2001.

This document is a review of efficacy information for resistant pathogens in the resubmission of the New Drug Application (NDA). In the resubmission, the applicant has requested approval for use of Ketek™ in the following indications:

- **Community-acquired pneumonia** due to *S. pneumoniae*, including strains resistant to penicillin G and/or the macrolides, *H. influenzae* (including ß-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains), *S. aureus*, *C. pneumoniae*, *L. pneumophila*, and/or *M. pneumoniae*.
- **Acute bacterial exacerbation of chronic bronchitis** due to *S. pneumoniae* including strains resistant to penicillin G and/or the macrolides, *H. influenzae* (including ß-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains), and/or *S. aureus*.
- **Acute sinusitis** due to *S. pneumoniae,* including strains resistant to penicillin G and/or the macrolides, *H. influenzae* (including ß-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains), and/or *S. aureus*.

Acute Exacerbation of Chronic Bronchitis (AECB) is addressed in the clinical review by Alma Davidson, M. D. Her review describes the studies of AECB in the original NDA and the resubmission. This document does not address that indication.

The main subject of this review is the efficacy of Ketek™ in the treatment of patients with drug-resistant *Streptococcus pneumoniae* (DRSP). As evidence, the applicant collected clinical cases of patients with community-acquired pneumonia (CAP) and acute sinusitis (ABS) due to DRSP from the phase 3 trials of Ketek™. To provide the appropriate background for assessing these claims, the remainder of this introductory section will summarize the results of the CAP and ABS trials in the original NDA submission.

Acute Bacterial Sinusitis (ABS)

The following section summarizes ABS data submitted with the original NDA application, as amended. No new studies of ABS were provided in the NDA resubmission.

Two studies, 3002 and 3005, were included in the original NDA submission as pivotal trials for the treatment of acute bacterial sinusitis (ABS). Study 3002 compared two different durations of telithromycin in a trial primarily designed to gather outcome data in subjects with microbiologically confirmed ABS. There was no comparator in this trial. Study 3005 was a comparative study in subjects with a clinical diagnosis of sinusitis. Study 3011 was submitted in a major amendment to the original NDA. It was submitted in order to bolster the number of patients with ABS due to drug-resistant *S. pneumoniae*. This study employed sinus puncture in US patients for microbiological

diagnosis. Table 1.1 provides basic information about the pivotal ABS trials in the original NDA.

Table 1.1: Study Information for Pivotal ABS Trials in the Original NDA

Protocol	Study Type	Dose/Frequency/Duration	N*	Countries
Study 3002[1]	Multicenter, randomized, double-blind, uncontrolled trial including sinus puncture	Telithromycin 800 mg qd for 5 d Telithromycin 800 mg qd for 10 d	167 168	Austria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Sweden
Study 3005[2]	Multicenter, randomized, controlled, three-arm trial	Telithromycin 800 mg qd for 5 d Telithromycin 800 mg qd for 10 d Amox/Clav 500/125 mg tid for 10 d	201 204 202	Argentina, Canada, Chile, S. Africa, US *(US patients 64.3%)*
Study 3011[1,2,3]	Multicenter, randomized (2:1), double-blind, controlled trial including sinus puncture in US	Telithromycin 800 mg qd for 5 d Cefuroxime axetil 250 mg bid for 10 d	240 116	France, S. America, S. Africa, US *(US patients 56.4%)*

[1] *These studies were primarily intended to study patients who had maxillary sinus punctures for bacteriologic studies.*
[2] *Patients from two investigative sites were excluded from the FDA analyses due to concerns about data integrity.*
[3] *Submitted to the NDA as part of a major amendment on February 20, 2001. Additional case-report forms were submitted on March 05, 2001.*
* *Number of patients in MITT population*

All three studies enrolled patients based on clinical signs and symptoms as well as radiological findings. The studies differed in the radiological criteria used for enrollment. Patients in all three studies could be enrolled with total opacification or air fluid levels on sinus X-ray. Patients with mucosal thickening of ≥6 mm could be enrolled in Study 3005. Patients with mucosal thickening of ≥10 mm could be enrolled in Study 3011. All three studies employed placebo dummy capsules to maintain blinding.

Table 1.2 summarizes the FDA analysis of clinical outcomes at the TOC visit for the defined populations. The TOC visit was scheduled for days 17 to 24. Clinical outcomes (cure, fail, or indeterminate) at the TOC visit were assigned based on resolution or improvement in clinical findings, no worsening of radiological findings, and no need for subsequent antimicrobial treatment during the study.

Table 1.2: ABS Clinical Responses at the TOC Visit (Original NDA)

	Telithromycin 5-Days			Comparators 10-Days				2-sided 95% Confidence Interval
	N	Cure	%	Comparator	N	Cure	%	
PPc Population								
Study 3002 [1]	123	112	91.1	TEL 10-D [2]	133	121	91.0	(-7.7%, 7.9%)
Study 3005	146	110	75.3	AMC [2]	137	102	74.5	(-9.9%, 11.7%)
Study 3011	189	161	85.2	CXM [2]	89	73	82.0	(-7.1%, 13.4%)
PPb Population								
Study 3002	70	65	92.9	TEL 10-D	69	63	91.3	(-10.3%, 7.4%)
Study 3005	7	5	87.5	AMC	8	6	66.7	(-48.5%, 41.4%)
Study 3011	100	84	84.0	CXM	49	38	77.6	(-8.8%, 21.0%)
MITT Population								
Study 3002	167	138	82.6	TEL 10-D	168	147	87.5	(-13.1%, 3.3%)
Study 3005	201	140	69.7	AMC	202	138	68.3	(-8.2%, 10.9%)
Study 3011	240	193	80.4	CXM	116	84	72.4	(-2.2%, 18.2%)

[1] *Study 3002 compared two dosing regimens of TELITHROMYCIN (5 days vs. 10 days).*
[2] *TEL 10-D = telithromycin 10-Days, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil*

In the PPc population, efficacy rates differed between studies for telithromycin treatment. The higher clinical response rates in Study 3002 may be related to treatment bias, since it was known that all subjects received telithromycin (whether for 5 or 10 days). On the other hand, the lower response rates in Study 3005 are more difficult to assess without microbiological confirmation of ABS. However, the lower rates were seen in both the telithromycin and comparator patients.

Reasons for excluding patients in the MITT population from the PPc populations were: previous antibiotic therapy, insufficient treatment duration, incorrect entry diagnosis, lost to follow-up, no X-ray within 2 days of entry into study, baseline laboratory abnormality followed by treatment discontinuation.

Table 1.3 shows the FDA analysis of bacteriologic outcome in these studies.

Table 1.3: Bacteriologic Outcome (Cure) by Pathogen in ABS – PPb Population at Post-Therapy/TOC (Single and Mixed Isolates)

Pathogen	Telithromycin 5 d	Telithromycin 10 d	Amox/Clav	Cefuroxime
S. pneumoniae	49/55 (89.1%)	24/26 (92.3%)	2/4 (50%)	12/12 (100%)
H. influenzae	36/42 (85.7%)	12/12 (100%)	1/1 (100%)	12/14 (85.7%)
M. catarrhalis	12/13 (92.3%)	3/4 (75%)	1/1 (100%)	6/6 (100%)

The Applicant has requested the indication of acute sinusitis due to *S. pneumoniae,* including penicillin- and erythromycin-resistant strains. Table 1.4 shows the FDA analysis of telithromycin efficacy across the three ABS studies in the PPb population for drug-resistant *S. pneumoniae*. This analysis was presented before the Anti-Infective Drugs Advisory Committee in April of 2001.

The definition of the breakpoints for *S. pneumoniae* follows:

Penicillin		Erythromycin	
Susceptible	< 0.06 µg/ml	Susceptible	< 0.25 µg/ml
Intermediate	0.12 < MIC < 1 µg/ml	Intermediate	0.25 < MIC < 1 µg/mL
Resistant	≥ 2 µg/ml	Resistant	≥ 1 µg/ml

Table 1.4: Outcome in ABS due to *S. pneumoniae* by resistance pattern in telithromycin-treated patients (PPb population, 3 studies combined)

Study #	Outcome – Cured					
	Pen-S	PRSP	Ery-S	Ery-R	Pen-S + Ery-S	PRSP+ Ery-R
3002	32/37 (86.5%)	3/3 (100%)	30/34 (88%)	7/8 (87.5%)	30/34 (88%)	3/3 (100%)
3005	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
3011	10/12 (83%)	7/9 (77.8%)	9/11 (82%)	10/12 (83.3%)	9/11 (82%)	5/7 (71.4%)
TOTAL	44/51 (86.3%) *12 mixed* (10/12, 83%)*	11/13 (84.6%) *2 mixed (2/2, 100%)*	41/47 (87%) *12 mixed 9/12 (75%)*	18/21 (85.7%) *5 mixed (5/5, 100%)*	41/47 (87%) *11 mixed (10/11, 91%)*	9/11 (82%) *2 mixed (2/2, 100%)*

** mixed - cultures which contained bacterial pathogens in addition to S. pneumoniae*

The applicant requested an indication for 5-day treatment of sinusitis with telithromycin. Across sinusitis studies, there were 10 patients with PRSP isolated in the 5-day treatment groups. The clinical success rate in this group was 80% (8/10). There were 4 patients with PRSP isolates in the cefuroxime axetil group in study 3011, and all were considered cures.

(M. O. Comment: The results shown in Table 1.2 were considered substantial evidence of efficacy for telithromycin treatment of ABS. The by pathogen results in Table 1.3 were consistent with those of other products approved for ABS. However, as noted in the excerpts from the approvable letter, further information to support the use of telithromycin for DRSP was needed.)

Community-Acquired Pneumonia (CAP)

The original NDA submission included both blinded, comparative studies and open-label, non-comparative studies of telithromycin for the treatment of CAP. These trials were designed to include patients with mild-to-moderate CAP. There were specific exclusion criteria to limit the enrollment of patients with characteristics of severe CAP (e.g., respiratory rate >30, need for parenteral antibiotics) or other risk factors for serious infection (e.g., neoplastic disease, HIV infection) in most trials. The length of treatment varied from 7 to 10 days, depending on the design of the trial. Table 1.5 provides

summary information about the pivotal and supportive trials for CAP in the original NDA.

Table 1.5: Study Information for Pivotal and Supportive CAP Trials in the Original NDA

STUDY	DESIGN	TREATMENT	DAYS	N**	GEOGRAPHIC REGION
Pivotal Comparative Studies					
3001	Multicenter, double-blind, randomized, active-controlled, Comparative, 2-arm parallel group	Telithromycin 800 mg po qd Amoxicillin 1000 mg po tid	10 d 10 d	404	Argentina, Australia, Austria, Finland, France, Germany, Hungary, New Zealand, South Africa, Spain, Sweden, UK, Uruguay
3006	Multicenter, double-blind, randomized, Active-controlled, Comparative	Telithromycin 800 mg po qd Clarithromycin 500 mg po bid	10 d 10 d	416	USA, Canada, Argentina, Chile
3009*	Multicenter, double-blind, randomized, Active-controlled, Comparative	Telithromycin 800 mg po qd Trovafloxacin 200 mg po qd	7 - 10 d 7 - 10 d	204	USA, Canada, South Africa
Supportive Non-Comparative Studies					
3000	Multicenter, open-label, non-comparative	Telithromycin 800 mg po qd	7 - 10 d	240	Argentina, Australia, Austria, Belgium, Finland, France, Germany, Hungary, Israel, New Zealand, Norway, South Africa, Sweden
3009OL	Multicenter, Open-label, Non-comparative	Telithromycin 800 mg po qd	7 - 10 d	212	South Africa
3010	Multicenter Open-label, Non-comparative	Telithromycin 800 mg po qd	7 d	418	USA, South America, South Africa, Canada

** This study was terminated prematurely because of safety concerns with the comparator, trovafloxacin.*

*** Number of patients in MITT population*

Study 3001 is a multi-national study performed outside of the United States. The dose of amoxicillin is based on treatment recommendations in Europe. This amoxicillin dose is higher than the FDA labeled dose for lower respiratory tract infections. Study 3009 was converted to an open-label trial, study 3009OL, when restrictions were placed on the use of trovafloxacin. Study 3010 was submitted in a major amendment to the original NDA, in order to increase the number of CAP patients with drug-resistant *S. pneumoniae.*

The clinical response (cure, fail, or indeterminate) was generally assigned at a test-of-cure (TOC) visit, usually 7-10 days after the end of treatment. Patients who failed treatment at an earlier visit were assigned an outcome of failure at the TOC visit. Table 1.6 summarizes the FDA analysis of clinical outcomes at the TOC visit for the pivotal and supportive studies:

Table 1.6: CAP Clinical Responses at the TOC Visit (Original NDA)

	Telithromycin				Comparators[1]				2-sided 95% Confidence Interval
	Regimen	N	Cure	%	Regimen	N	Cure	%	
PPc Population*									
Study 3001	TEL 10 d	149	141	94.6	AMX 10 d	152	137	90.1	(-2.1%, 11.1%)[2]
Study 3006	TEL 10 d	162	143	88.3	CLA 10 d	156	138	88.5	(-7.9%, 7.5%)[2]
Study 3009	TEL 7-10 d	80	72	90.0	TVA 7-10 d	86	81	94.2	(-13.6%, 5.2%)[2]
Study 3000**	TEL 7-10 d	197	183	92.9	-	-	-	-	
Study 3009OL**	TEL 10-d	187	175	93.6	-	-	-	-	
Study 3010**	TEL 7 d	357	332	93.0	-	-	-	-	
MITT Population*									
Study 3001	TEL 10 d	199	171	85.9	AMX 10 d	205	161	78.5	(-0.5%, 15.3%)[2]
Study 3006	TEL 10 d	204	161	78.9	CLA 10 d	212	171	80.7	(-9.9%, 6.5%)[2]
Study 3009	TEL 7-10 d	100	82	82.0	TVA 7-10 d	104	89	85.6	(-14.7%, 7.5%)[2]
Study 3000**	TEL 7-10 d	240	191	79.6	-	-	-	-	
Study 3009OL**	TEL 7-10 d	212	182	85.8	-	-	-	-	
Study 3010**	TEL 7 d	418	357	85.4	-	-	-	-	

* *PPc = Clinical Per-protocol Population, MITT = Modified Intent-to-treat Population*

** *Studies which did not include an active control arm*

[1] *TEL = telithromycin, AMX = amoxicillin, CLA= clarithromycin, TVA = trovafloxacin,*

[2] *Confidence interval for the difference of the two cure rates.*

Table 1.7 provides the FDA analysis of bacteriological eradication and clinical cure rates for patients whose baseline culture(s) grew the reported pathogen. In general, the bacteriological responses are determined based on clinical outcome. Most subjects reported as clinical cures no longer produce sputum samples, and most clinical failures are categorized as having presumed persistence of the baseline pathogen.

Table 1.7: Bacteriological Eradication and Clinical Cure Rates at the TOC Visit for Telithromycin-Treated Patients in the PPb* Population

Causative pathogen	Bacteriological eradication			Clinical cure		
	N	Cure	(%)	N	Cure	(%)
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)

* *PPb = Bacteriological Per-protocol Population*

The original NDA did include some data regarding telithromycin treatment of CAP due to drug-resistant *S. pneumoniae*. This information is not repeated here. A later section of this review will integrate old and new data regarding telithromycin treatment of CAP due to drug-resistant *Streptococcus pneumoniae*.

Table 1.8 provides the FDA analysis of clinical outcomes in CAP patients meeting specific serologic criteria for these atypical pathogens. Comparator patients received either clarithromycin or trovafloxacin.

Table 1.8: Clinical Cure Rates at the TOC Visit for Atypical Pathogens Based on Serologic Diagnosis

Pathogen	Telithromycin 7-10 Days			Comparators 7-10 Days		
	N	Cure	%	N	Cure	%
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%)

* *Includes controlled CAP studies 3006, 3009 and uncontrolled CAP studies 3000, 3009OL and 3010.*
** *Only five cases were documented by urinary antigen; the others were diagnosed by serum antibody titers.*

(M. O. Comment: The overall results in table 1.6 were felt to provide substantial evidence of efficacy for telithromycin treatment of mild to moderate CAP. The by pathogen results for telithromycin-treated patients in the PPb population are shown.)

2. *Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or Other Consultant Reviews*

Andrew Yu, Ph. D., completed the chemistry review for the original NDA and the resubmission. The chemistry reviewer recommended approval from the chemistry perspective. Telithromycin is derived [redacted] Ketek™ tablets are light-orange, oval, film-coated tablets, each containing 400 mg of telithromycin, plus the following inactive ingredients: cornstarch, croscarmellose sodium, [redacted], lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide. The tablets are available in bottles of 60 tablets. There is also the Ketek Pak™, a 10-tablet blister card with 2 tablets (the daily dose) per blister cavity. The storage conditions proposed are 25°C (77°F). The expiration period for the tablets is 3 years, based on real-time studies of product stability.

Terry Peters, D.V.M., completed the toxicology review. The findings from animal studies are relevant to the safety evaluation of telithromycin, and are addressed in that review.

Fred Marsik, Ph. D., completed the microbiology review of the original NDA. Harold Silver, B.S., reviewed the additional microbiological data in the resubmission. Ketolides, including telithromycin, are a new class of antibacterial agents that are structurally related to macrolides (erythromycin, clarithromycin) and azalides (azithromycin). The mode of action for telithromycin is inhibition of protein synthesis by interaction with the 50S subunit of bacterial ribosomes. The MIC_{90} for selected organisms are shown below:

- *S. pneumoniae* (including penicillin- and erythromycin-resistant stains): 0.25 μg/mL
- *H. influenzae* (β-lactamase -negative: 2 μg/mL; β-lactamase-positive: 4 μg/mL)
- *M. catarrhalis* (including β-lactamase-positive strains): 0.5 μg/mL
- *S. pyogenes* (erythromycin-susceptible: 0.06 μg/mL; erythromycin-resistant: 8 μg/mL)

Telithromycin has also provided evidence of in vitro activity against atypical pathogens, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila.*

The in vitro activity of telithromycin against macrolide-resistant strains of *Streptococcus pneumoniae* is of particular interest. The following table shows the distribution of telithromycin MIC's for clinical isolates of *S. pneumoniae* from the studies of community-acquired pneumonia. This table does not include the clinical isolates of S. pneumoniae from the Japanese studies of CAP, because susceptibility test results were not provided for all *S. pneumoniae* isolates. The reviewer used isolates from CAP studies for convenience. The results are not expected to be different for clinical isolates of S. pneumoniae from other studies. The table presents the MIC distribution for ERSP separately from erythromycin-susceptible or -intermediate strains. The heavy line

indicates the MIC_{90} of telithromycin for *S. pneumoniae*. Of note, the telithromycin MICs for ERSP strains appear to be higher than for most *S. pneumoniae* strains.

Table 2.1: Distribution of Telithromycin MIC's for CAP clinical isolates of *Streptococcus pneumoniae* from Western Studies – PPb Population

Telithromycin MIC (µg/mL)	Erythromycin Susceptible and Intermediate Strains	ERSP
	N	N
N/A	32	--
0.004	4	
0.008	125	
0.016*	112	1
0.03	14	9
0.06	1	5
0.12	1	5
0.25	--	1
0.5	--	3
1	--	5
Total	289	29

** Data for MIC values of 0.015 and 0.016 µg/mL have been pooled.*

(M. O. Comment: While there is a shift in the MICs for telithromycin against ERSP strains compared to other *S. pneumoniae* isolates, most MICs are below the applicant's proposed breakpoint for telithromycin. The clinical outcomes for CAP patients with ERSP are discussed in a later section of this review. However, there does not appear to be a direct correlation between higher telithromycin MIC and treatment failure in CAP patients.

The mechanisms of erythromycin resistance in these CAP isolates include both ribosomal methylation and the efflux pump. The highest telithromycin MICs (≥0.25 µg/mL) do not appear to be associated with one particular mechanism of erythromycin resistance.)

Telithromycin is inactive against most Enterobacteriaceae, *Pseudomonas* spp., and other non-fermentative Gram-negative bacilli. Activity against *Staphylococcus aureus* and other *staphylococci* is variable. Most methicillin-resistant strains of *S. aureus* are resistant to telithromycin. The MIC_{90} of *S. aureus* for telithromycin from the applicant's PROTEKT surveillance program is ≥64 µg/mL.

George Rochester, Ph. D., was the statistical reviewer for the original NDA. The statistical reviewer for the resubmission was Thamban Valappil, Ph. D. The statistical analyses presented by the applicant for the phase 3 studies have been confirmed by the statistical reviewers. Much of the data in the Integrated Summary of Efficacy was generated in collaboration with Dr. Valappil.

3. Human Pharmacokinetics and Pharmacodynamics

The reader should refer to the Clinical Pharmacology and Biopharmaceutics reviews of the original NDA and the NDA resubmission by Jenny Zheng, Ph. D. for detailed information. Numerous studies were performed to characterize the pharmacokinetics of Ketek™ (telithromycin) 400-mg oral tablets. The absolute bioavailability was approximately 57% in an absorption study. No food effects were noted. In a study of metabolism and excretion, roughly 22% and 12% of telithromycin was recovered unchanged in the feces and urine. Telithromycin is metabolized by the cytochrome P450 system, in particular as a substrate of CYP 3A4. Several studies of drug interactions have been performed. Of particular note, telithromycin concentrations are increased in the presence of CYP3A4 inhibitors. Telithromycin also appears to be a weak CYP3A4 inhibitor, increasing the concentrations of drugs metabolized by CYP3A4. **(M. O. Comment: The reader should refer to the clinical pharmacology review for a thorough discussion of the drug interactions with Ketek™)**

The pharmacokinetics of telithromycin is non-linear, with greater than dose proportional increases in AUC and C_{max} with increasing dose. The accumulation factor was roughly 1.5 after multiple doses. The following table shows mean PK values following a single dose or multiple doses in a study from the original NDA submission.

Table 3.1: Mean (CV) values for PK parameters from Study 1008

Single dose:	Multiple doses:
C_{max} (mg/L)= 1.90 (42); Range:	C_{max} (mg/L)= 2.27(31); Range:
$AUC_{0-\infty}$ (mg*h/L)= 8.25 (31)	$AUC_{0-\infty}$ (mg*h/L)= 12.5 (43) Range:
$t_{½}$ (h): 7.16 (19)	$t_{½}$ (h): 9.81 (20)
CL/F (L/h): 102.3 (31) Range:	CL/F (L/h): 71.1 (29) Range:
CLr/F_{0-24} (L/h): 12.32 (17)	CLr/F (L/h): 12.5 (34)

Source: Clinical Pharmacology and Biopharmaceutics Review of Original NDA 21-144

There were no effects of gender on PK. AUC and C_{max} increased in the elderly, but the applicant did not recommend any dosage adjustment. In subjects with hepatic impairment, AUC and C_{max} were comparable. Again, no dosage adjustment was recommended. AUC and C_{max} increased in subjects with severe renal impairment after a single dose and after multiple doses. For severe renal impairment, the applicant has

In the resubmission, the applicant submitted a study involving co-administration of telithromycin with ketoconazole in elderly subjects in order to investigate the effects on drug metabolism. The applicant also performed a study using supra-therapeutic doses of telithromycin in healthy subjects to investigate the visual adverse events associated with the drug.

4. Description of Clinical Data and Sources

A. Overall Data

New clinical data used in this review were provided in a resubmission of NDA 21-144 in response to the FDA approvable letter. The resubmission was received by the FDA on July 24, 2001. It included final study reports, case report forms and case report tabulations in an electronic format. An integrated summary of efficacy, pulling together information from the original NDA submission with new efficacy studies in the resubmission was also provided. Section 4B outlines the new efficacy studies that are data sources for this review. Final study reports and supporting materials for other studies of safety, AECB, and pharmacokinetics were included in the resubmission. These trials are the subject of other reviews, and are not described here.

Some clinical data within this review are derived from the studies of community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) submitted by the applicant with the original NDA. The trials of CAP and ABS from the original NDA review were described briefly in the introduction and background section. The final study reports for those trials were submitted with the original NDA or with an NDA amendment. The FDA received the final study reports for CAP studies 300, 3001, 3006, and 3009 on February 28, 2000. The final study reports for ABS studies 3002 and 3005 were also received in this submission. This submission included copies of case report forms and case report tabulations for the listed studies in an electronic format. FDA received CAP study 3010 and ABS study 3011 in an amendment to the original NDA on December 20, 2000. This amendment included final study reports and case report forms for these studies. This amendment also included a report, in English, related to a Japanese study of pneumonia. The report included an English translation of the protocol, a summary of the overall findings, and patient narratives for selected patients with DRSP. Scanned copies of the case report forms in the original Japanese were also included.

B. Tables Listing the Clinical Trials

Table 4.1 on the following page provides summary information about the new efficacy trials in the NDA resubmission that are used in this document. All of these clinical trials were for treatment of CAP. There were no new ABS studies provided by the applicant.

Table 4.1: Study Information for CAP Trials in the NDA Resubmission

STUDY	DESIGN	TREATMENT	DAYS	N*	GEOGRAPHIC REGION
3012	Open label	Telithromycin 800 mg po qd	7 d	538	USA, Argentina, France, Mexico, South Africa, Spain
4003	Multicenter, Double-blind, randomized, active-controlled, 3-arm, parallel group	Telithromycin 800 mg po qd Telithromycin 800 mg po qd Clarithromycin 500 mg po bid	5 d 7 d 10 d	559	USA, Argentina, Brazil, Canada, Chile, Germany, South Africa, Spain, UK
3107	Multicenter, double-blind, randomized, active-controlled, comparative	Telithromycin 600 mg po qd Levofloxacin 100 mg po tid	7 d 7 d	237	Japan

** Number of patients in MITT population*

C. Post-Marketing Experience

Ketek™ has been approved in the European Union and several other countries. Post-marketing information has been submitted to the FDA in the form of adverse event reports, but these reports do not contribute additional efficacy information. For information on post-marketing experience, the reader should refer to the safety review by Charles K. Cooper, M. D.

D. Literature Review

On January 13, 2002, the reviewer performed a literature search using telithromycin as the search term on the National Library of Medicine's PubMed website. There were 201 items retrieved in this search. The vast majority of these publications (>90%) were reports of the in vitro activity against a variety of pathogens or animal model studies. The remaining reports fell into one of the following categories: publications based on the studies performed by the applicant, including the efficacy trials and pharmacokinetic studies; review and opinion articles about telithromycin, or the ketolide class of antibiotics; and studies of the mechanism of action on bacterial ribosomes.

For efficacy, the published literature does not appear to provide additional significant information. For the most part, the published literature is based on PK, microbiology, and efficacy studies performed by the applicant.

5. Clinical Review Methods

A. How the Review was Conducted

To address the main question in this review, efficacy of Ketek™ for treatment of drug-resistant *S. pneumoniae*, the reviewer gathered information from multiple efficacy studies. Some of these studies had been reviewed in the original NDA submission for Ketek™. The reviewer read through the pertinent clinical reviews of the original NDA and accessed study reports, case report forms, case report tabulations, etc. in the applicant's electronic submission of the original NDA.

The reviewer read through information about CAP and DRSP provided in the resubmission (described in section 4A of this clinical review) received on July 24, 2002. The protocols for the newly submitted studies ("Western" studies 3012 and 4003; Japanese study 3107) were compared with the CAP study protocols in the original NDA submission and NDA amendments in the first cycle of review ("Western" studies 3000, 3001, 3006, 3009, 3009 OL, and 3010; Japanese study 2105). CAP and ABS analyses from the original NDA review were also summarized. The summary is provided in the introduction to this clinical review.

Summaries of the new CAP studies are provided in Appendices A and B of this document. The information in these summaries is excerpted from the applicant's reports. In appendix A, the reviewer also provides some comparisons to the CAP studies in the original NDA. The reviewer concluded that the Western studies were substantially similar in design, methodology, selection criteria, and outcome definitions. These study elements are consistent with the recommendations for CAP studies in FDA's draft Guidance for Industry. Minor variations, as noted in the appendix, may affect the comparability of the study populations across trials, but do not prohibit gathering cases of CAP due to DRSP from across studies. Results from open-label and comparative trials can be combined, but should also be analyzed separately.

Appendix B describes the new Japanese study 3107. Few comments compare this trial to the other Japanese study 2105, but the limitations are similar with both. The reviewer concluded that the cases of CAP due to DRSP in the Japanese trials could be used as supportive evidence, but it was inappropriate to combine the Japanese cases with those from Western studies. The reader is referred to Appendix B for a discussion of the limitations of these data.

The data from the original NDA were considered adequate to support an overall indication of CAP. Since the main object of this review was to determine the efficacy of telithromycin for CAP due to DRSP, the medical officer did not perform a traditional review of the overall CAP results for the new studies. Instead, the reviewer focused on the analysis of DRSP cases.

Working with the statistical reviewer, all cases of CAP due to DRSP were identified from the clinical trials. The applicant was also asked to provide a list of DRSP cases along with information on the MICs, evaluability, and outcome to confirm that all cases were identified. The medical officer reviewed the case report forms or patient profiles for all cases of CAP due to DRSP. Some information was also obtained from the tabulated data provided by the applicant in SAS transport files. The reviewer made an independent assessment of the evaluability and outcome for each of these cases. In particular, the patients with clinical outcomes of failure or indeterminate were reviewed in detail. Appendix C provides narratives for telithromycin-treated patients in these categories. Appendix D provides narratives for all comparator patients with DRSP, since they were relatively few in numbers. The overall analysis of outcomes for CAP patients with DRSP and the write-up of this review followed.

B. Overview of Materials Consulted in Review

The materials used in the review are outlined in Sections 4A and B of the clinical review.

C. Overview of Methods used to Evaluate Data Quality and Integrity

The review of the original NDA included inspections of nine investigator sites by the Division of Scientific Investigations (DSI). As a result, data from six sites were censored. For the resubmission, the DSI inspections were focused on the large safety trial. These inspections should be addressed in the safety review. DSI did receive information on the investigators in the efficacy trials.

Since the main subject of this review is the activity of telithromycin in CAP patients with DRSP, the reviewer investigated the source of the different isolates. No single investigator accounted for more than three patients with CAP due to DRSP. None of the patients were from censored sites. The reviewer read through the case report forms for all the CAP patients with DRSP. There were no "for cause" inspections initiated.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The applicant states in the final study reports for these trials that they were conducted in accordance with Good Clinical Practice guidelines. The applicant provides a list of institutional review boards/independent ethics committees that reviewed and approved the protocols and protocol amendments. The applicant stated that informed consent was obtained from patients prior to the conduct of any study-related procedures.

E. Evaluation of Financial Disclosure

For the resubmission, there were no investigators that reported significant financial interests for studies 1064, 3012, 3013, or 4003. The applicant provided a signed copy of form FDA 3454 certifying that no financial arrangements as defined in 21 CFR 54 were entered into with the listed investigators.

6. Integrated Review of Efficacy

COMMUNITY-ACQUIRED PNEUMONIA

Cases of CAP due to drug-resistant *S. pneumoniae* (DRSP) were identified from the clinical trials submitted by the applicant. The main body of evidence to support PRSP and ERSP claims comes from studies conducted in Western countries ("Western studies"). These are studies 3000, 3001, 3006, 3009, 3009OL, 3010, 3012, and 4003. Studies 3012 and 4003 were provided to the FDA in the NDA resubmission on July 27, 2001. Although the studies varied in the duration of telithromycin treatment and blinding, the selection criteria, timing of visits, outcome definitions, and other study methods were fairly similar. The following breakpoints were used to define penicillin and erythromycin resistance in *S. pneumoniae* strains:

Penicillin		Erythromycin	
Susceptible	< 0.06 μg/ml	Susceptible	< 0.25 μg/ml
Intermediate	$0.12 <$ MIC ≤ 1 μg/ml	Intermediate	$0.25 <$ MIC < 1 μg/mL
Resistant	≥ 2 μg/ml	Resistant	≥ 1 μg/ml

(M. O. Comment: The applicant performed susceptibility testing on all pathogens isolated in clinical trials at a central laboratory. The susceptibility testing was performed according to methodology recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Penicillin and/or erythromycin resistance based on testing at the central lab was used as the basis for inclusion of patients in the population with DRSP.)

A. DRSP in Western CAP Studies

Table 6.1 provides the applicant's analysis of clinical outcome at the TOC visit in the bacteriological per protocol population. There were 37 patients with CAP due to DRSP in the bacteriological per protocol (PPb) population.

Table 6.1: Applicant Analysis of Clinical Outcome for CAP Patients with *Streptococcus pneumoniae* at the TOC Visit – PPb Population

	All Western Studies		
	N	Cure	(%)
All *S. pneumoniae*	318	300	(94.3)
Pen-R	19	16	(84.2)
Ery-R	29	25	(86.2)
Pen-R and Ery-R	11	8	(72.7)
Pen-R or Ery-R*	26	25	(96.2)

**Excludes patients in the Pen-R and Ery-R category*
Source: ISE page 21 - NDA resubmission, July 24, 2001

(M. O. Comment: It should be noted that these are not mutually exclusive categories. For instance, some patients in the Pen-R category are included in each

of the three following rows. The applicant's presentation focused on the bacteriological per protocol population for all CAP studies. Results for the MITT population are not shown, because they were not provided in the main body of the ISE. Patients from blinded trials are shown together with those from open-label studies. Most of the subjects are from open-label, non-comparative studies.)

Table 6.2 provides the FDA analysis of clinical cure rates for telithromycin-treated CAP patients from all Western Studies with drug-resistant *Streptococcus pneumoniae* isolated from baseline cultures (sputum and/or blood). Clinical outcome was assessed at the TOC visit. A total of 49 cases (MITT population) were identified where PRSP and/or ERSP were isolated. The table separates patients by resistance patterns. Results are shown for both the per-protocol and modified intent-to-treat populations. Of note, 16/28 (57.1%) PRSP isolates were also resistant to erythromycin.

The analysis of the bacteriological per protocol population is exactly the same as that presented by the applicant. It differs only in the format in which it is presented. In table 6.2, each category is mutually exclusive of the others within a population. For instance, adding all N for the PPb population (8 + 18 + 11 = 37) gives the total number of cases with CAP due to DRSP in that population. The patients within the PPb population are a subset of the patients in the MITT population. In this table, all indeterminate outcomes are treated as failures.

Table 6.2: Clinical Cure Rates in CAP Patients with Drug-Resistant *Streptococcus pneumoniae* by Resistance Pattern (Western Studies)

Study Population/ Resistance mechanism	Telithromycin 800 mg qd		
	N	Cure	%
PPb Population			
PRSP Only*	8	8	100
ERSP Only**	18	17	94.4
Both PRSP and ERSP***	11	8	72.7
MITT Population			
PRSP Only*	12	9	75.0
ERSP Only**	21	19	90.5
Both PRSP and ERSP***	16	10	62.5

** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC < 1 µg/ml*
*** Patients with isolates whose penicillin MIC < 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*
**** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

In cases with PRSP isolates (regardless of erythromycin resistance), the clinical cure rate was 16/19 (84.2%) in the per-protocol group and 19/28 (67.9%) in the MITT population. For cases with ERSP isolates (regardless of penicillin resistance), the clinical cure rate was 25/29 (86.2%) in the per-protocol group and 29/37 (78.4%) in the MITT population.

(M. O. Comment: Lower cure rates were seen in the MITT population than in the PPb population. In part, this is due to the fact that patients with an indeterminate outcome are automatically made non-evaluable. However, there is only one case, patient #3000/101/1365, in which an indeterminate outcome was appropriately assigned. The other cases should be considered failures, although this is a conservative action for some. The reviewer has provided narratives for the telithromycin-treated patients with outcomes of failure or indeterminate in Appendix C. These narratives are provided to give the reader a sense of the complexity of some cases. They also show that misdiagnoses of CAP and losses to follow-up are not driving factors for assigning patients to the MITT population.)

Table 6.3 provides the clinical cure rates for telithromycin-treated CAP patients with DRSP from the comparative trials.

Table 6.3: Clinical Cure Rates in CAP Patients with DRSP by Resistance Pattern from Comparative Studies+ (Western Studies)

Study Population/ Resistance mechanism	Telithromycin 800 mg qd			Comparators		
	N	Cure	%	N	Cure	%
PPb Population						
PRSP Only*	2	2	100	1	1	100
ERSP Only**	7	7	100	5	3	60
Both PRSP and ERSP***	2	1	50	--	--	--
MITT Population						
PRSP Only*	4	2	50	1	1	100
ERSP Only**	7	7	100	5	3	60
Both PRSP and ERSP***	2	1	50	1	1	100

+ Studies 3001, 3006, and 4003; There were no patients with PRSP or MRSP in the comparative portion of Study 3009

** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC < 1 µg/ml*

*** Patients with isolates whose penicillin MIC < 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

**** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

In the comparative studies (3001, 3006, 3009, and 4003), there were 7 comparator-treated patients with drug-resistant *S. pneumoniae* identified in baseline cultures. One amoxicillin-treated CAP patient had ERSP isolated from sputum. The isolate was susceptible to penicillin. She was considered cured at the TOC visit. One clarithromycin-treated CAP patient had PRSP identified in baseline cultures. The isolate was susceptible to erythromycin. He was considered cured at the TOC visit.

Five CAP patients with ERSP were treated with clarithromycin in the comparative trials. At the TOC visit, 4/5 were considered cured, though one of the clinical cures was noted to have a recurrence of pneumonia at a later follow-up visit. This patient (#3006/0013/001) was categorized as a failure by the reviewer based on the recurrence of symptoms.

(M. O. Comment: Narratives for the patients in the comparator group are provided in Appendix D. As noted previously, study 3009 was a comparative trial that was terminated early. Since there were no patients with drug-resistant S. pneumoniae isolates in the trial, it does not contribute to the results in Table 6.3. Few of the telithromycin-treated patients with DRSP were enrolled in the comparative trials.

The results for clarithromycin-treated patients lead to questions about granting claims for treatment of CAP due to macrolide-resistant *S. pneumoniae.* The cure rate for telithromycin-treated patients in comparative trials with CAP due to ERSP (regardless of penicillin-resistance) was 8/9. The applicant's cure rate for clarithromycin-treated patients with CAP due to ERSP (regardless of penicillin resistance) was 4/5. The reviewer's cure rate for clarithromycin-treated patients was 3/5, though for patient #3006/0013/001 the attribution of failure (late recurrence) to ERSP is reasonable to question. Whether the cure rate for clarithromycin-treated patients with CAP due to MRSP is 3/5 or 4/5, the point to be made is that many of these patients with CAP due to ERSP resolve their infection. Most of the patients in the CAP trials have mild to moderate illness, appropriate for oral antibiotic treatment. It should not be assumed that all or even most of the patients with CAP due to ERSP would have failed macrolide treatment.)

B. DRSP Bacteremia in Western CAP Studies

The FDA analysis of outcomes for CAP patients with pneumococcal bacteremia due to drug-resistant strains is shown in the following table. In CAP patients with bacteremia due to PRSP (regardless of erythromycin resistance), the clinical cure rate was 5/7 in the per-protocol group and 5/10 in the MITT population. For bacteremia due to ERSP (regardless of penicillin resistance), the clinical cure rate was 8/10 in the per-protocol group and 8/11 in the MITT population.

Table 6.4: FDA Analysis of Clinical Cure Rates in CAP Patients with Bacteremia due to DRSP by Resistance Pattern (Western Studies)

Study Population/ Resistance mechanism	Telithromycin 800 mg qd	
	N	Cure
PPb Population		
PRSP Only*	3	3
ERSP Only**	6	6
Both PRSP and ERSP***	4	2
MITT Population		
PRSP Only*	5	3
ERSP Only**	6	6
Both PRSP and ERSP***	5	2

** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC < 1 µg/ml*

*** Patients with isolates whose penicillin MIC < 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

**** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

The patients who are considered treatment failures in this analysis are #3000/101/1365, #3000/605/1091, #3001/0111/010, #3009OL/0369/105, and #3012/3019/001. Brief narratives for these patients are included in Appendix C of this review. This list does include one patient (#3000/101/1365) in the PRSP only group who was considered to have an indeterminate outcome. The remaining patients are considered to be treatment failures, including one with persistent bacteremia (#3009OL/0369/105) at an on-therapy visit.

One failure (Patient #4003/3212/003) of clarithromycin treatment was notable. This was the only clarithromycin-treated patient with bacteremia due to ERSP. This patient had CAP and ERSP with a MIC of 512 µg/mL isolated from blood culture. The patient was switched from study drug to gentamicin and ceftazidime on the fifth day of therapy due to worsening pneumonia and septic arthritis. This is a clear failure of clarithromycin treatment in a subject with ERSP bacteremia.

(M. O. Comment: As a reference, the applicant reported clinical cure rates at TOC in the PPb population of 74/82 (90.2%) for telithromycin-treated and 15/19 (78.9%) for comparator-treated CAP patients with *Streptococcus pneumoniae* (Pen-S, -I, and -R) bacteremia from Western studies. The applicant did not report the result for bacteremic patients in the ITT population. The numbers of CAP patients with DRSP bacteremia are too small to draw statistically-significant comparisons.

It is generally reassuring that most patients with DRSP bacteremia were clinical cures, despite the fact that they received oral antibiotic treatment. DRSP bacteremia in the presence of pneumonia provides added assurance that *S. pneumoniae* was the causative pathogen. However, bacteremia should not be taken as evidence that these patients were at increased risk of adverse outcome. Mortality risk, as measured by Fine class, was low for most of these patients. Among the telithromycin-treated patients with DRSP bacteremia, 9 were class I, 4 were class II, and 2 were class III. Both Fine class III patients were considered treatment failures.)

C. DRSP in Japanese CAP Studies

Additional cases of CAP due to PRSP and ERSP from two Japanese studies (studies 3107 and 2105) were provided as supportive evidence for these claims. These data are described separately for several reasons. First, these studies were conducted in Japanese patients, a population different from the "Western Studies" population in many respects. Most patients in the Japanese trials received a different, though lower, dose of telithromycin (600 mg qd) than that proposed for US patients. Finally, there were differences in the design of the Western and Japanese studies, including selection criteria and timing of the protocol-specified test of cure visit.

(M. O. Comment: As noted in Section 5A of this review, the Japanese data are viewed as supportive evidence and presented separately because of differences from the pivotal data. Appendix B provides a synopsis for the new Japanese study and a description of the differences with Western Studies.)

Table 6.5 provides the FDA analysis of clinical cure rates for telithromycin-treated CAP patients from Japanese studies with drug-resistant *Streptococcus pneumoniae* isolated from baseline sputum cultures. None of the patients in these trials had blood cultures. Although the Japanese protocols use the end-of-therapy visit for the TOC, clinical outcome was also assessed at a later visit (days 17-24).

Table 6.5: FDA analysis of Clinical Cure Rates in Telithromycin-Treated Patients with DRSP by Resistance Pattern (Japanese Studies)

Study Population/ Resistance mechanism	Telithromycin	
	N	Cure
PPb Population		
PRSP Only*	0	0
ERSP Only**	13	11
Both PRSP and ERSP***	8	8

** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC < 1 µg/ml*
*** Patients with isolates whose penicillin MIC < 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*
**** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

(M. O. Comment: These results are consistent with the clinical outcomes in the per protocol population from the Western studies. However, the reviewer is unable to independently confirm that these represent all cases of telithromycin-treated CAP patients with DRSP. MIC data were provided and confirmed only for the clinical isolates in the table. These data are taken as supportive of the results for the per-protocol population from the Western studies.)

D. Other Pathogens in CAP Studies

Other pathogens in the clinical studies of CAP were addressed briefly in the integrated summary of efficacy submitted by the applicant. Both bacteriological eradication rates and clinical cure rates by baseline pathogen were presented. The reviewer focused on the clinical outcomes by pathogen, because the bacteriological eradication results are typically driven by whether the clinical outcome was cure or failure. The clinical cures often have presumed bacteriological eradication, and failures often have presumed persistence of the baseline pathogen. The tables on the following page provide the clinical cure rates by pathogen as presented by the applicant. Though not shown in this review, similar analyses formed the basis for "by pathogen analyses" in the integrated summaries of Acute Exacerbation of Chronic Bronchitis and Acute Bacterial Sinusitis.

Table 6.6: Applicant's Analysis of Clinical Cure Rates at Post-Therapy/TOC by Pathogen in Telithromycin-Treated Subjects – PPb Population

	Clinical Cure											
	Previous Studies*			New Study (3012)			New Study (4003)					
							5 d			7 d		
	N	N	(%)	N	N	(%)	N	n	(%)	N	n	(%)
S. pneumoniae	174	165	(94.8)	90	83	(92.2)	24	23	(95.8)	30	29	(96.7)
H. influenzae	105	95	(90.5)	74	67	(90.5)	25	22	(88.0)	25	22	(88.0)
M. catarrhalis	30	26	(86.7)	14	12	(85.7)	1	1	(100)	5	5	(100)
S. aureus	19	15	(78.9)	15	12	(80.0)	5	5	(100)	5	4	(80.0)
Other	114	102	(89.5)	19	15	(78.9)	27	24	(88.9)	30	27	(90.0)
Total (all pathogens)	442	403	(91.2)	212	189	(89.2)	82	75	(91.5)	95	87	(91.6)

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.

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry.

n = subjects in the PPb population who were clinically cured.

**Includes controlled CAP Studies 3001 (vs. amoxicillin), 3006 (vs. clarithromycin), and 3009 (vs. trovafloxacin); and uncontrolled CAP Studies 3000, 3009OL, and 3010.*

Source: ISE page 19 - NDA resubmission, July 24, 2001

Table 6.7: Applicant's Analysis of Clinical Cure Rates at Post-Therapy/TOC by Pathogen in Telithromycin-Treated Subjects – PPb Population

	Clinical Cure		
	All CAP		
	N	n	(%)
S. pneumoniae	318	300	(94.3)
H. influenzae	229	206	(90.0)
M. catarrhalis	50	44	(88.0)
S. aureus	44	36	(81.8)
Other	190	168	(88.4)
Total (all pathogens)	831	754	(90.7)

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.

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry.

Source: ISE page 19 - NDA resubmission, July 24, 2001

(M. O. Comment: The applicant presents these results, noting high clinical cure rates. However, there are several limitations to the presented analyses. The results for telithromycin-treated patients are shown, but the results for the comparator patients are not provided. The applicant's analyses focus on the results in the bacteriological per-protocol population. However, the results for the MITT patients with a baseline pathogen are not discussed. The results shown combine the rates from blinded, comparative studies with open-label, non-comparative studies. The analyses shown also combine cases where the listed pathogen was the sole pathogen isolated with cases where multiple pathogens were isolated. Separate analyses

where the listed pathogen is the sole pathogen isolated would be useful for better estimating the effect of telithromycin in such cases. The reviewer recommends that the applicant provide more detailed analyses of clinical outcome by pathogen, taking into account the limitations discussed above.)

The reviewer had performed an analysis of clinical outcome for patients with CAP due to *H. influenzae* from the controlled studies. The following table provides the clinical outcome at the test-of-cure visit for patients with CAP due to *H. influenzae*. Results are shown for both the PPb and MITT populations. Results are also shown for cases where *H. influenzae* was the sole pathogen identified and where it could be one of multiple pathogens.

Table 6.8: FDA Analysis of Clinical Outcome for CAP Patients with *Haemophilus influenzae* at the TOC Visit in Controlled Trials*

Study Population/ *H. influenzae* Isolation	Telithromycin		Comparators	
	N	Cure (%)	N	Cure (%)
PPb				
Single Pathogen	24	19 (79.2)	27	26 (96.3)
Single or Multiple Pathogen	48	40 (83.3)	46	44 (95.6)
MITT				
Single Pathogen	55	39 (70.9)	52	43 (83.0)
Single or Multiple Pathogen	87	66 (75.8)	77	66 (86.0)

** Includes studies 3001, 3006, 3009, and 4003*

(M.O. Comment: The results suggest lower clinical cure rates for telithromycin-treated patients with CAP due to *H. influenzae*. If analyses by the applicant show confirm these results for CAP and possibly the other indications,

The applicant investigated the activity of telithromycin in the treatment of CAP patients with *Mycoplasma pneumoniae*, *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*, and *Legionella pneumophila*. Serology was investigated for all these pathogens. Polymerase chain reaction (PCR) testing was carried out for some patients with *Mycoplasma* and *Chlamydophila*. Urinary antigen testing was used for *Legionella*. The following tables provide the clinical cure rates by pathogen as presented by the applicant.

Table 6.9: Applicant's Analysis of Clinical Outcome at Post-Therapy/TOC by Atypical Pathogen in the PPc Population/Previous Studies

	Previous Studies*					
	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
Chlamydophila pneumoniae	**34**	**32**	**(94.1)**	**18**	**17**	**(94.4)**
Fourfold increase in IgG	31	29	(93.5)	15	15	(100.0)
Fourfold increase in IgM	5	5	(100.0)	3	3	(100.0)
Single IgM with positive PCR	1	1	(100.0)	1	0	(0.0)
Mycoplasma pneumoniae	**31**	**30**	**(96.8)**	**19**	**18**	**(94.7)**
Fourfold increase in IgG	27	26	(96.3)	14	13	(92.9)
Single IgM with positive PCR	6	6	(100.0)	5	5	(100.0)
Legionella pneumophila	**12**	**12**	**(100.0)**	**3**	**2**	**(66.7)**
Fourfold increase in IgG	9	9	(100.0)	2	2	(100.0)
Positive urinary antigen	4	4	(100.0)	1	0	(0.0)

N = number of subjects; n = number clinically cured.
**Includes controlled CAP Studies 3001 (vs. amoxicillin), 3006 (vs. clarithromycin), and 3009 (vs. trovafloxacin); and uncontrolled CAP Studies 3000, 3009OL, and 3010.*
Source: ISE page 38 - NDA resubmission, July 24, 2001

Table 6.10: Applicant's Analysis of Clinical Outcome at Post-Therapy/TOC by Atypical Pathogen in the PPc Population/New Studies

	New Studies								
	3012			4003					
	Telithromycin			Telithromycin			Comparators		
	N	N	(%)	N	n	(%)	N	N	(%)
Chlamydophila pneumoniae	NA*			**2**	**2**	**(100)**	**1**	**1**	**(100)**
Fourfold increase in IgG				0	0	(0.0)	0	0	(0.0)
Fourfold increase in IgM				2	2	(100)	1	1	(100)
Single IgM with positive PCR				0	0	(0.0)	0	0	(0.0)
Mycoplasma pneumoniae	NA*			**6**	**6**	**(100)**	**3**	**2**	**(66.7)**
Fourfold increase in IgG				5	5	(100)	3	2	(66.7)
Single IgM with positive PCR				1	1	(100)	1	1	(100)
Legionella pneumophila	**0**	**0**	**(0.0)**	**1**	**1**	**(100)**	**0**	**0**	**(0.0)**
Fourfold increase in IgG				1	1	(100)			
Positive urinary antigen				0	0	(0.0)			

N = number of subjects; n = number clinically cured.
**Study 3012 did not test for Chlamydophila pneumoniae or Mycoplasma pneumoniae.*
Source: ISE page 38 - NDA resubmission, July 24, 2001

Table 6.11: Applicant's Analysis of Clinical Outcome at Post-Therapy/TOC by Atypical Pathogen in the PPc Population/All CAP Studies

Pathogen/ Method of Identification	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
Chlamydophila pneumoniae	**36**	**34**	**(94.4)**	**19**	**18**	**(94.7)**
Fourfold increase in IgG	31	29	(93.5)	15	15	(100)
Fourfold increase in IgM	7	7	(100)	4	4	(100)
Single IgM with positive PCR	1	1	(100)	1	0	(0.0)
Mycoplasma pneumoniae	**37**	**36**	**(97.3)**	**22**	**20**	**(90.9)**
Fourfold increase in IgG	32	31	(96.9)	17	15	(88.2)
Single IgM with positive PCR	7	7	(100)	6	6	(100)
Legionella pneumophila	**13**	**13**	**(100)**	**3**	**2**	**(66.7)**
Fourfold increase in IgG	10	10	(100)	2	2	(100)
Positive urinary antigen	4	4	(100)	1	0	(0.0)

N = number of subjects; n = number clinically cured.
Source: ISE page 39 - NDA resubmission, July 24, 2001

(M. O. Comment: Some of the same limitations noted with the bacterial pathogen analyses also apply to the data presented on these atypical pathogens. The small number of patients with *Legionella pneumophila* from all CAP studies is of particular note. As seen from table 6.9, the numbers of patients with atypical pathogens from individual studies are fairly low. The reviewer recommends that the applicant provide more detailed analyses by pathogen, as requested for the bacterial pathogens. The reviewer did perform a more detailed analysis of the small number of *Legionella* cases.)

The applicant was asked to provide tables of all CAP patients with *Legionella pneumophila* based on serologic or urinary antigen testing. Both urinary antigen testing and serologic testing with an indirect immunofluorescence assay (IFA) were used in the various studies to detect patients with *Legionella*. The following table provides the numbers of patients in each of the CAP studies in whom testing was performed.

Table 6.12: Number of Telithromycin-Treated Patients Tested for Legionella in CAP Trials

Study Number	IFA Testing	Urinary Antigen Testing
3000	187	221
3001	188	188
3006	7	176
3009/3009OL	33	287
3010	47	345
3012	0	60
4003	247	0
Total	**709**	**1277**

Source: Aventis e-mail response, dated Jan. 6, 2003, to an information request

(M. O. Comment: In these studies of oral outpatient treatment of CAP, a total of 1540 patients were tested for *Legionella*. Urinary antigen testing was not performed in Study 4003. In Study 3012, *Legionella* testing was initiated by protocol amendment late, so only a small proportion of the patients in the trial were tested. There were 1277 patients in whom urinary antigen testing was performed. The reviewer will use 709 patients as the number of patients tested by IFA. However, screening by enzyme immunoassay (EIA) was conducted in Studies 3006 and 3009/3009OL. Only subjects with positive results on EIA from convalescent blood samples were tested by IFA. Thus, the number of subjects screened for serologic conversion in acute/convalescent titers is likely higher.)

The following table provides the clinical outcomes for telithromycin-treated patients in the CAP trials with positive tests for *Legionella*. Patients were included in the urinary antigen group if they had a single positive result. Patients were included in the IFA group if there was a four-fold rise in titer from acute to convalescent samples. Only three telithromycin-treated patients were positive by both IFA and urinary antigen. All three of these patients were considered cured. The patients in the PPc group are a subset of the MITT population.

Table 6.13: Clinical Outcome in Telithromycin-Treated CAP Patients who Tested Positive for Legionella

Study Population/ Test Method	Telithromycin	
	N	Cure
PPc		
Urinary Antigen	5	5
IFA	10	10
MITT		
Urinary Antigen	8	6
IFA	11	11

N= Number of Patients; Cure= number with clinical outcome of success at the TOC visit
Source: Aventis e-mail response, dated Jan. 6, 2003, to an information request

There were 5 patients in the comparator group who tested positive for *Legionella pneumophila*. Three amoxicillin-treated patients in the PPc population were positive for Legionella based on urinary antigen testing. Two of these three patients were considered cured. In study 3006, two clarithromycin-treated patients were positive for *Legionella* by serology. One was in the PPc population and considered cured. The second was in the MITT population with an indeterminate outcome (considered a failure in this analysis).

(M. O. Comment: The small number of patients with positive test results relative to the number of subjects tested suggests that most of these patients do not have *Legionella* infections. The specificity of the IFA test was reported by the applicant to be approximately . Reports indicate that cross reacting antibodies can develop with *Bacteroides*, *Campylobacter*, and *Pseudomonas*. The applicant also reported the specificity of the urine antigen test as . However, the urinary antigen test is reported to have a specificity of in a retrospective study

and [redacted] in a prospective study[1]. Using these specificities, the number of false positives expected for each test can be estimated. The number of false positives/total tested should be roughly equal to [redacted] specificity. For the urinary antigen test, a specificity of [redacted] means that the number of false-positive is expected to be 0-63 patients given the number of patients tested. For the IFA test, a specificity of [redacted] means that 7 false-positive results are expected for the number of patients tested. If the number of patients screened using an EIA were added, the number of expected false positives would be higher.

The three patients with positive results on both IFA and urinary antigen test probably have mild Legionnaire's disease. (Positive results by more than one test method are more suggestive of true disease.) However, it seems likely that most of the remaining cases are patients with false-positive results. Legionnaire's disease is typically thought of as a severe pneumonia unresponsive to penicillins or aminoglycosides, although milder forms of disease are known. Telithromycin is available only in an oral tablet formulation, and the studies of CAP involved patients with mild to moderate pneumonia appropriate to outpatient treatment.

Based on the above analysis, the medical officer does not recommend inclusion of *Legionella pneumophila* as an organism under the community-acquired pneumonia indication. In order to include *Legionella* as part of a CAP indication, studies should be designed to specifically enrich for patients likely to have that pathogen. Widespread testing of a large population for a low-prevalence disease leads to high numbers of false-positive tests.)

ACUTE BACTERIAL SINUSITIS

As noted in the introduction to this clinical review, there were no new studies of acute bacterial sinusitis (ABS) in the resubmission. Three studies of acute bacterial sinusitis were provided in the original NDA submission. The results of the three studies of ABS in the original submission (studies 3002, 3005 and 3011) are described briefly in the introduction. The introduction includes the applicant's analysis of outcomes in subjects with ABS due to drug-resistant *S. pneumoniae*.

A. DRSP in ABS Studies

The table on the following page provides the FDA analysis of clinical cure rates for telithromycin-treated ABS patients with drug-resistant *Streptococcus pneumoniae* isolated from baseline cultures (sinus aspirates). This analysis is in the same format as that used in the preceding analysis of CAP patients with DRSP. The same breakpoints were used to identify penicillin- and erythromycin-resistant strains of *S. pneumoniae*. Clinical outcome was assessed at the TOC visit. A total of 29 cases (MITT population) were identified where PRSP and/or ERSP were isolated. The table separates patients by resistance patterns. Results are shown for both the per-protocol and modified intent-to-treat populations.

[redacted]

Table 6.14: Clinical Cure Rates in ABS Patients with Drug-Resistant Streptococcus pneumoniae by Resistance Pattern

Study Population/ Resistance mechanism	Telithromycin 800 mg qd	
	N	Cure
PPb Population		
PRSP Only*	2	2
ERSP Only**	10	9
Both PRSP and ERSP***	11	9
MITT Population		
PRSP Only*	3	3
ERSP Only**	13	10
Both PRSP and ERSP***	13	11

** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC < 1 µg/ml*
*** Patients with isolates whose penicillin MIC < 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*
**** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≥ 1 µg/ml*

In cases with PRSP isolates (regardless of erythromycin resistance), the clinical cure rate was 11/13 (84.6%) in the per-protocol group and 14/16 (87.5%) in the MITT population. For cases with ERSP isolates (regardless of penicillin resistance), the clinical cure rate was 18/21 (85.7%) in the per-protocol group and 21/26 (80.7%) in the MITT population. It should be noted that the subjects with indeterminate outcomes (2 MITT subjects) are counted as failures in this analysis.

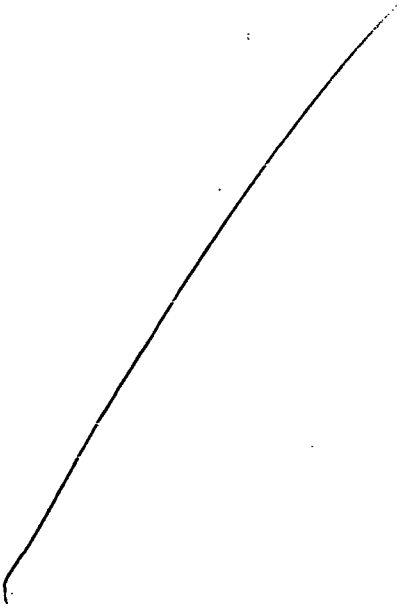
Nine of these twenty nine subjects were from study 3002, in which all subjects were treated with telithromycin. Subjects in study 3002 were randomized to 5 days or 10 days of antibiotic treatment. The table does not distinguish between those subjects who received 10 days of telithromycin and those who received 5 days of telithromycin. The majority of subjects with ABS due to DRSP received the shorter course of therapy.

Most comparator-treated patients with ABS due to DRSP received cefuroxime axetil. The outcome for cefuroxime-treated patients was 6/7. The failure was a cefuroxime-treated subject in the MITT population with an indeterminate outcome. There was one patient in the MITT population of study 3005 with ABS due to PRSP (MIC 2 µg/ml) and treated with amoxicillin/clavulanate (500 mg of amoxicillin TID). This subject was categorized as a treatment failure.

(M. O. Comment: The point estimates for clinical outcome in subjects with ABS due to DRSP are slightly below the rates for ABS due to any *S. pneumoniae*, but the numbers of subjects are too few to draw statistically significant conclusions. The numbers of subjects with ABS due to DRSP are less than the numbers with CAP due to DRSP. However, the lower numbers are not the main reason that the medical officer is recommending against granting a separate claim for ABS due to PRSP and MRSP. The subject treated with amoxicillin/clavulanate was a 34 year-old male who completed treatment and appeared to be improved at the end-of-therapy visit, but

returned with a sore throat seven days after completion of study drug treatment. He was diagnosed with "Strep throat" and treated with amoxicillin. The treatment with other antibiotics led to classification as a treatment failure.)

B. Labeling Claims for Resistant Pathogens in ABS



In summary, the medical officer does not recommend approval of a separate labeling claim for treatment of PRSP or ERSP in acute bacterial sinusitis. In ABS, the treatment effect of antibiotics is not well-defined. Given such questions about the efficacy of antibiotics in this disease, there is little basis for separate resistance claims in ABS. Data to support the occurrence of adverse clinical outcomes as a consequence of penicillin or macrolide treatment of ABS due to DRSP are lacking.

7. Integrated Review of Safety

The reader should refer to the safety review by Charles K. Cooper, M. D., and the analysis of Study 3014, a large safety trial reviewed by George Rochester, Ph. D., for detailed information.

The safety profile of Ketek™ (telithromycin) includes some adverse events typical of anti-bacterial drugs and other rare concerning findings. Common adverse events include diarrhea, nausea, headache, vomiting, and dyspepsia. These AE occurred at rates similar to comparator agents in the controlled phase 3 trials. Particular safety concerns with Ketek™ fall into three categories, as described in the following paragraphs.

This drug has been shown to prolong the QTc interval based on results from in vitro studies of myocytes, animal studies, and Phase 1 studies in humans. These studies demonstrated a small, but reproducible effect. The effect on QTc was shown to be concentration-dependent. ECG data from controlled phase 3 studies showed a mean change in QTc on therapy of 1.5 ± 22.3 ms for telithromycin-treated patients and -2.0 ± 23.3 ms for comparator patients.

Visual adverse events associated with telithromycin treatment were first identified in the phase 3 trials. The overall incidence of blurred vision was roughly 0.5% among telithromycin-treated patients in the phase 3 trials. The incidence appeared higher among young women, although both genders and elderly patients were affected. Studies of a single 2400-mg dose of telithromycin (three times the recommended daily dose) in healthy subjects were performed to study this effect. The incidence of blurred vision was higher in these patients. The effect has been described as a delay in accommodation. There were no significant changes on ophthalmologic examination at the time of the event. Reports of significant impairment to vision have been received in post-marketing from other countries. The visual disturbances appear to resolve in most cases with discontinuation of the drug.

Animal studies demonstrated hepatotoxic effects in several species. The safety reviews provide a thorough discussion of the hepatic effects of Ketek™ in humans. The applicant has provided a large safety study in an attempt to address the risk for significant hepatic injury. However, it is likely that such questions may only be addressed through post-marketing surveillance in a large population.

8. Dosing Regimen and Administration Issues

The dosage of Ketek™ in the phase 3 efficacy trials is 800 mg (two tablets) given orally one time daily. The duration is 7 to 10 days for community-acquired pneumonia, and 5 days for sinusitis and acute exacerbation of chronic bronchitis.

9. Use in Special Populations

The efficacy studies of Ketek™ were performed in adults with community-acquired pneumonia, acute exacerbation of chronic bronchitis, tonsillitis/pharyngitis, and acute sinusitis. The applicant provided subgroup analyses of the overall results by age group, gender, and race for each of the three indications. There was no indication of differences in efficacy of Ketek™ based on these demographic factors. Patients in the ≥65 age group were noted with somewhat lower cure rates than younger patients, but this was also seen in patients treated with comparator drugs. The numbers of patients with drug-resistant pathogens are too few to draw conclusions from similar subgroup analyses.

However, in all phase 3 studies there were a total of 59 adolescent patients (ages 13 through 17 years). There were 21 adolescent patients in the CAP studies, and 5 adolescents in the sinusitis trials. The others were from tonsillitis/pharyngitis studies. As expected, there were no adolescent patients with AECB. No pediatric clinical trials have been performed as yet. The pharmacokinetics of Ketek™ in pediatric patients (including adolescents) have not been studied.

As noted in section 3 of this review, some PK studies were performed in patients with hepatic impairment and renal impairment. Patients with hepatic impairment are expected to have comparable exposure to Ketek™ at the recommended doses.

10. Conclusions and Recommendations

The applicant has previously provided substantial evidence of efficacy for telithromycin in the treatment of mild to moderate community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS). A labeling claim for CAP due to PRSP is approvable, once sufficient evidence of the safety of telithromycin has been provided. This recommendation is based on: 1) the in vitro data that show the mechanism of action of telithromycin is unaffected by penicillin-resistance in *S. pneumoniae*; 2) the previous finding of efficacy for telithromycin in the treatment of CAP (including penicillin-susceptible strains of *S. pneumoniae*); 3) clinical cure rates for CAP due to PRSP of 84.2% (16/19) in the evaluable population and 70.4% (19/27) in the MITT population; 4) the precedent for approval of other products with this claim; and 5) the benefit of an alternative to quinolone treatment for CAP due to PRSP.

The medical officer does not recommend approval of a separate claim for MRSP. The main basis for this recommendation is the lack of evidence to support the clinical impact of MRSP, as a distinct entity from PRSP, on morbidity or mortality in CAP. The applicant should be asked to provide evidence of the separate public health impact of MRSP in the CAP indication. With such evidence, the Agency could consider separate labeling for MRSP or a claim for treatment of CAP due to multi-drug resistant *S. pneumoniae*. The inclusion of other pathogens in CAP is approvable, with the exception of *Legionella pneumophila*. However, the applicant should provide more detailed analyses showing clinical outcomes at the TOC visit for each labeled pathogen:

- by indication (CAP, ABS, or AECB);
- showing bacteriological per-protocol and MITT population results;
- with controlled and uncontrolled studies presented separately;
- including the comparator outcomes for controlled studies;
- with sensitivity analyses of indeterminate outcomes as missing or failure.

The reviewer does not recommend inclusion of *Legionella pneumophila* in the CAP indication. The majority of reported cases of CAP due to *L. pneumophila* are likely to be cases of outpatient CAP with false-positive test results.

The reviewer does not recommend approval for PRSP or MRSP claims in Acute Bacterial Sinusitis. The reviewer does not think there is adequate justification for a separate claim for PRSP or MRSP in this indication. The high spontaneous resolution rate for patients with ABS limits the conclusions that can be drawn from the small number of subjects with ABS due to PRSP or MRSP. There is little information available in the literature on the treatment effect of antibiotics in the indication of ABS, but it is likely small. Given this small treatment effect, there is little basis for separate claims of added effectiveness against drug-resistant pathogens.

APPENDICES

Appendix A: Study Synopses of the new Western Studies

HMR3647A/3012

Study Title: An open-label, multicenter, multinational, uncontrolled study of the efficacy and safety of 7 days of oral telithromycin (800 mg once daily) in the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* in adolescents and adults.

Primary Objective: To evaluate the clinical and bacteriological efficacy of 7 days of oral telithromycin in the treatment of CAP due to *S. pneumoniae* resistant to penicillin G and/or erythromycin A (macrolides) in adolescents and adults.
Secondary Objective: To evaluate the clinical and bacteriological efficacy of 7 days of oral telithromycin in the treatment of CAP due to *S. pneumoniae* in adolescents and adults. To evaluate the clinical and bacteriological efficacy of 7 days of oral telithromycin in the treatment of CAP in adolescents and adults.

Study Design: This was an open-label, multicenter uncontrolled study of oral telithromycin treatment of community-acquired pneumonia (CAP). Subjects were enrolled at 68 investigational sites in the following countries: Argentina (9 sites), France (9 sites), Mexico (3 sites), South Africa (17 sites), Spain (4 sites), and the US (26 sites). The first patient was enrolled on Feb. 21, 2001 and the last patient for whom data were submitted enrolled on Jan. 18, 2002. A total of 622 patients were enrolled, and 550 received at least one dose of telithromycin.

The study included 4 scheduled study visits: an entry visit on day 1, an on therapy visit on days 3-5, an end-of-therapy visit on days 8-10, and a test-of-cure visit on days 17-21.

Treatment: Telithromycin 800 mg (2 x 400-mg tablets) once daily for 7 days.

Primary efficacy data: clinical outcome in the PPc population and bacteriological outcome in the PPb population at the posttherapy/TOC visit.
Secondary efficacy data: clinical outcome in the MITT population and bacteriological outcome in the bMITT population at the posttherapy/TOC visit.

HMR 3647A/4003

Study Title: Double-blind, active-controlled study of the efficacy and safety of oral telithromycin (HMR 3647 800 mg once daily) 5 days versus 7 days versus 10 days oral clarithromycin (500 mg twice daily) in the treatment of community-acquired pneumonia (CAP).

Primary objective: To demonstrate equivalence in clinical efficacy at the posttherapy/test of cure (TOC) visit and assess the safety of 5 days and 7 days of oral telithromycin (800 mg given once daily) and 10 days of oral clarithromycin (500 mg given twice daily) for treating CAP due to common or atypical and intracellular pathogens in adults.
Secondary objective: To compare bacteriological efficacy of 5 days and 7 days of oral telithromycin and 10 days of oral clarithromycin for treating CAP due to common or atypical and intracellular pathogens in adults.

Study Design: 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). Subjects were enrolled at a total of 77 investigational sites in the following countries: Argentina (8 sites), Brazil (5 sites), Canada (14 sites), Chile (2 sites), Germany (6 sites), South Africa (9 sites), Spain (4 sites), United Kingdom (5 sites) and United States (24 sites). The study took place between December 29, 1999 and April 20, 2001. A total of 581 subjects were enrolled and 575 subjects were randomized to one of the three treatment groups. All of the 575 randomized subjects received at least one dose of study medication as follows: telithromycin 5-day group: 193 subjects, telithromycin 7-day group: 195 subjects, and clarithromycin 10-day group: 187 subjects.

There were five visits: a pretherapy/entry visit (day 1), an on-therapy visit (days 3 to 5), an end-of-therapy visit (days 11 to 13), a posttherapy/test of cure (TOC) visit (days 17 to 21) and a late posttherapy visit (days 31 to 36).

Treatments:
1. Telithromycin: 800 mg (2 x 400-mg capsules) once daily for 5 days (*2 x 400 mg capsules) Plus matching placebo for 5 days
2. Telithromycin: 800 mg (2 x 400-mg capsules) once daily for 7 days (*2 x 400 mg capsules) Plus matching placebo for 3 days
3. Clarithromycin: 500 mg (2 x 250-mg capsules) twice daily for 10 days (*2 x 250 mg capsules)

Primary efficacy data: clinical outcome at the posttherapy/TOC visit in the PPc population.
Secondary efficacy data: bacteriological outcome at the posttherapy/TOC visit in the PPb population, and clinical and bacteriological outcomes at late posttherapy in the PPc and PPb populations, respectively.

(M. O. Comment: The above descriptions of study 4003 and 3012 are excerpted from the final study reports. The methodologies and designs are consistent in with the FDA's draft guidance for CAP. No significant differences were noted between the designs of the new studies 4003 and 3012 and the controlled and uncontrolled studies in the original NDA, respectively. The timing of study visits, the data collection methods, the selection criteria, even the format and language used in the protocols were almost exactly alike through the TOC visit. Late post-therapy visits were not included in al trials, but this is a minor point. The only major differences

in the protocols were the open label treatment course for the uncontrolled studies, the different comparators (amoxicillin in study 3001, trovafloxacin in study 3009, and clarithromycin in studies 3006 and 4003), and the different treatment durations used for telithromycin (generally 7-10 days, except for a 5-day treatment arm in study 4003). The remainder of this appendix provides the selection criteria and planned efficacy analysis from the final report for study 4003. Comments by the reviewer note differences between stud 4003 and study 3012.)

Inclusion criteria

Subjects meeting all of the following criteria were considered for admission to the study:

- Adult hospitalized or outpatient subjects, male and female, aged 18 years or greater; **(M. O. Comment: The age range in study 3012 started at 13 years. The studies in the original NDA all used age 18 as the starting age.)**
  - For female subjects, the following criteria were to be met:
    - postmenopausal for at least 1 year, or
    - surgically incapable of bearing children, or
    - of childbearing potential, and all of the following conditions were met:

      normal menstrual flow within 1 month before study entry,

      And

      negative pregnancy test (serum β-sub-unit hCG) immediately before study entry (i.e., before the start of treatment or any other study procedure that could potentially harm the fetus). If obtaining the serum pregnancy test result would have caused a delay in treatment, the subject was to be entered on the basis of a negative urine pregnancy test sensitive to at least 50 mU/mL, pending results of the serum pregnancy test. Subsequently, if the result of the serum test was positive, the subject was to be discontinued from study medication, and every attempt was to be made to follow such subjects to term,

      And

      Agreed to use an accepted method of contraception (i.e., oral or implanted contraceptive, spermicide and barrier method, or IUD). The subject must have agreed to continue with the same method throughout the study.

- Subjects with diagnosis of acute CAP based upon:
  - Production of purulent sputum

    And
  - Chest x-ray findings supporting a clinical diagnosis of bacterial pneumoniae (e.g., presence of presumable new infiltrate). Subjects could have been enrolled based upon investigator assessment of x-ray but confirmation by a local board-certified radiologist was required.

    And
  - New onset of **at least two** of the following clinical signs and symptoms:
    - Cough
    - Auscultatory finding such as rales and/or evidence of pulmonary consolidation (i.e., dullness on percussion, bronchial breath sounds, egophony)

- Dyspnea or tachypnea, particularly if progressive in nature
- Fever - oral temperature >38°C (100.4°F) or tympanic temperature >38.5°C (101.2°F) or rectal temperature >39°C (102.2°F)
- Elevated total peripheral white blood cell count >10,000/mm 3 or >15% immature neutrophils (bands), regardless of total peripheral white count

- Subjects were required to have specimens collected for bacteriological documentation within 48 hours prior to enrollment. Specimens were to include the following:
  - Respiratory/sputum samples for evaluation and testing via Gram stain, cultures, antimicrobial susceptibility testing and PCR testing for atypical and intracellular pathogens (i.e., *Chlamydophila (Chlamydia) pneumoniae* and *Mycoplasma pneumoniae*)
  - Blood samples, for evaluation and testing by culture and serology

  Subjects were to be enrolled before Gram stain or microbiological results were available.

(M. O. Comment: Serologic testing for atypical pathogens was not done in study 3012, but it did include urine samples for antigen detection of *S. pneumoniae* and *L. pneumophila*. The latter was added by an amendment to protocol 3012. The studies in the original NDA also varied with regard to testing for atypical pathogens by serology and/or urinary antigen for *L. pneumophila*, urine antigen detection of *S. pneumoniae*. Sputum and blood specimens for culture and sputum Gram stain were standard in all the CAP studies.)

Informed consent was to be obtained for all subjects before enrollment in the study.

(M. O. Comment: The following bullet is used in study 3012 in place of the second bullet above for diagnosis of CAP. Study 3010 used the same bullet except that urinary antigen testing for S. pneumoniae was not done.)

From the final study report for 3012:

- Subjects with diagnosis of acute CAP based upon:
  - New onset of at least two of the following Group A and Group B clinical signs and symptoms, one of which must have been from Group A:

  Group A
  - Fever (oral temperature >38°C [100.4°F] or tympanic temperature >38.5°C [101.2°F] or rectal temperature >39°C [102.2°F])
  - Chills
  - Pleuritic chest pain
  - Elevated total peripheral white blood cell (WBC) count >10,000/mm 3 or >15% immature neutrophils (bands)
  - Gram stain showing gram-positive diplococci from a sputum or respiratory secretion specimen
  - Positive [redacted] *S. pneumoniae* urinary antigen test

Group B

- Cough
- Production of purulent sputum or a change in sputum character
- Auscultatory findings (such as rales [also known as crepitations] and/or evidence of pulmonary consolidation [i.e., dullness on percussion, bronchial breath sounds, egophony])
- Dyspnea or tachypnea (particularly if progressive in nature)

and

- Chest x-ray findings which support a clinical diagnosis of bacterial pneumonia (e.g., presence of presumably new infiltrate[s]). Subjects were to be enrolled based upon the investigator's assessment of the x-ray. Confirmation of the diagnosis of pneumonia was required by a local board certified radiologist.

(M. O. Comment: The criteria for diagnosis in the comparative CAP studies in the original NDA were similar to those for study 4003. These differences in inclusion criteria are minor, as can be seen by comparing the bullet for study 3012 and study 4003. Some differences may lead to subtle differences in the enrolled patients for different studies. For example, the requirement for production of purulent sputum in study 4003 may lead to a higher enrollment of subjects with COPD. The use of urinary antigen testing for *S. pneumoniae* in study 3012may increase the proportion of patients with pneumococcal disease. However, all studies include patients who meet clinical and radiological criteria for CAP. In review of case report forms from the different studies, all studies collected data on the same baseline signs and symptoms. Overall, the reviewer considered the study populations to be comparable across trials.)

Exclusion criteria

Subjects meeting any of the following criteria were not to be included in the study:

- Subjects with CAP requiring either intensive care unit (ICU) admission, parenteral antibiotic treatment, or at least one of the following conditions:
  - Resting respiratory frequency >30 breaths/minute
  - Chest radiograph (x-ray) showing an increase in the size of the opacity by ≥50% within 48 hours of the current evaluation
  - Shock (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg)
  - Altered mental status (disorientation to person, place or time that was not known to be chronic, lethargy, stupor or coma)
  - <90 O_2 saturation (by pulse oximetry) or a PaO_2 <60 mmHg
  - Total peripheral white blood cell count <4000/mm^3
  - Required mechanical ventilation
  - Required vasopressors for more than 4 hours
  - Urine output lower than 20 mL/hr or total urine output lower than 80 mL in 4 hours, unless another explanation was available, or acute renal failure requiring dialysis

(M. O. Comment: In study 3012, hypothermia was also included in the above list of exclusionary findings.)

- Subjects with respiratory tract infections (RTIs) attributable to sources other than community-acquired bacterial infection, including:
  - Ventilator-associated pneumonia
  - Nosocomial pneumonia (defined as: pneumonia occurring in subjects who were hospitalized for ≥72 hours, within the 7 days preceding entry into the study)
  - Visible/gross aspiration pneumonia
  - Suspected nonbacterial RTIs (e.g., suspected active or latent viral infections or fungal infections).
- Subjects with any concomitant pulmonary disease, condition or complications that could have confounded the interpretation or evaluation of drug efficacy or safety, including:
  - Subjects suffering from severe bronchiectasis, cystic fibrosis, known or suspected active pulmonary tuberculosis, suspected exacerbation of allergic pulmonary diseases, suspected acute pulmonary infarction or pulmonary embolism
  - Empyema, lung abscess, extra pulmonary extension (e.g., meningitis, septic arthritis, endocarditis)
  - Subjects with known bronchial obstruction or a history of postobstructive pneumonia (this did not exclude subjects who had chronic obstructive pulmonary disorder).
- Subjects with neoplastic lung disease (lung cancer) or another malignancy metastatic to the lungs, and/or required chemotherapeutic interventions for this or other neoplasms.
- Subjects receiving other medications, including other systemic antimicrobial agents, or who had other disease conditions or infections that could have interfered with the evaluation of drug efficacy or drug safety.
- Subjects who had received more than 24 hours of treatment with other antibiotics, within the 7 days prior to enrollment in the study.
- Subjects treated within the 7 days prior to enrollment with any macrolide antibiotic or ceftriaxone.

(M. O. Comment: Study 3012 allowed exceptions to the above criterion if the patient was unsuccessfully treated and CAP due to S. pneumoniae was suspected.)

- Subjects who had a microbiologically documented infection with a pathogen known prior to inclusion to be resistant to the study medications.

(M. O. Comment: The above bullet was not used in study 3012. It appears intended to exclude patients with known macrolide-resistant pathogens prior to study drug treatment.)

- Females who were breast-feeding or were pregnant, as demonstrated by serum or urine pregnancy tests carried out before exposure to study medication or the start of any study procedure that could pose a risk to the fetus.
- Subjects with known or suspected hypersensitivity to, or a known or suspected serious adverse reaction to the study medications (telithromycin or clarithromycin) or macrolide antibiotics.
- Subjects with progressively fatal disease (e.g., life expectancy ≤3 months).

- Subjects who required on-study treatment with medications known to have contradicted drug interactions with the study medication and/or macrolides in general, including but not limited to:
  - Ergot alkaloid derivatives, terfenadine, cisapride, astemizole, pimozide, cholinesterase inhibitors (e.g., tacrine, donepezil, physostigmine), ketamine and quinidine.
- Subjects who received any investigational drug within 1 month prior to study entry or such treatment was planned for during the study period.
- Subjects who had a known long QTc syndrome or severe hypokalemia.
- Subjects with any concomitant condition, including clinically relevant cardiovascular, neurologic, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult.

(M. O. Comment: Patients with "clinically relevant cardiovascular disease" were allowed into study 3012 by protocol amendment.)

- Subjects with a recent (within the previous 3 months) history of drug or alcohol abuse.
- Subjects with impaired hepatic function (e.g., previous clinical laboratory values of SGOT/AST and/or SGPT/ALT ≥4 times the upper limit of the reference range, total bilirubin >2 times the upper limit of reference range [except for Gilbert's disease] or encephalopathy).

(M. O. Comment: The above bullet was not part of study 3012. The studies in the original NDA did have similar exclusions for hepatic impairment.)

- Subjects with impaired renal function as shown by creatinine clearance ≤50 mL/min [≤0.83 mL/sec] (creatinine clearance could have been estimated by formula or nomogram provided in the protocol).
- Immunocompromised subjects, such as:
  - Subjects with HIV infection and, had either an AIDS-defining condition (e.g., Kaposi's sarcoma, *Pneumocystis carinii* pneumonia (see protocol for a complete list of AIDS-defining events) or had a CD4 + T-lymphocyte count of <200/mm^3. Note for clarification: subjects who were HIV positive without an AIDS defining condition and CD4 + T-lymphocyte count >200/mm^3 were allowed to participate in this study.
  - Subjects with neutropenia (<1500 neutrophils/mm^3) not attributable to the acute infectious disease
  - Subjects with metastatic or hematological malignancy
  - Splenectomised subjects or subjects who had known hyposplenia or asplenia
  - Subjects on maintenance corticosteroid therapy (>10 mg/day equivalent prednisone).
- Subjects with a mental condition rendering them unable to understand the nature, scope, and possible consequences of the study.
- Subjects unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study).

Subjects were enrolled before clinical laboratory results were available.

Any waiver of the above inclusion and exclusion criteria was to be approved by the investigator and the applicant on a case-by-case basis prior to enrolling the subject. This was to be documented by both the applicant and the investigator.

Subjects were not allowed to enroll in this study more than once.

(M. O. Comment: Study 3012 also specifically excluded any patient who had previously been treated with telithromycin. The few differences in exclusion criteria between studies 4003 and 3012 are noted. Similar variations are seen with exclusion criteria from studies in the original NDA. However, these differences are minor and do not have an impact on efficacy. It should be noted that the applicant specifically excluded patients with characteristics of severe pneumonia, or risk factors for mortality from pneumonia. These are appropriate for the development of an oral antibiotic. However, labeling should reflect that mild to moderate pneumonia was studied if the product is approved.)

Analytic Populations

Population	Definition
MITT	All randomized subjects, as treated, with a confirmed diagnosis of infection who received at least one dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and X-ray findings, as defined in the protocols. This definition was intended to exclude subjects with a clear misdiagnosis, in whom study medication could have no 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.

Source: ISE page 4 – NDA Resubmission, July 24, 2002

Outcome Definitions at the Test of Cure (TOC) visit
(M. O. Comment: The following definitions for clinical outcomes at the TOC visit are from the final study report for study 4003. The same definitions were used for study 3012. There were no significant differences in these definitions for CAP studies in the original NDA.)

Clinical Cure

- **Return to preinfection state**: all pneumonia-related signs and symptoms had disappeared or had returned to the preinfection state and chest x-ray findings showed improvement.

  Or

- **Improved or postinfectious stigmata**: residual symptoms that did not warrant any treatment and that represented the normal clearance of the inflammatory

process; residual mild pneumonia-related signs and symptoms, residual signs and symptoms related to underlying condition/disease and not related to pneumonia, chest x-ray findings showed improvement or lack of progression, and no subsequent antibiotic therapy was started for treatment of the disease under investigation.

Clinical Failure

- All pneumonia-related signs and symptoms had remained unchanged or had worsened and/or chest x-ray findings had worsened.

  Or

- One or more antibiotics or subsequent treatment was added to the study treatment for the pneumonia due to lack of clinical improvement.

  Or

- The subject developed new clinical findings consistent with active infection.

  Or

- The subject died due to the infectious disease.

  Or

- A new antibiotic treatment was started up to the end of day 21 for the treatment of CAP, bronchitis, any other lower RTI or an infection at another relevant site that could have indicated a complication of CAP (e.g., meningitis, sepsis).

  Or

- An adverse event other than CAP, bronchitis, any other lower RTI or an infection at another relevant site that could have indicated a complication of CAP (e.g., meningitis, sepsis) occurred on therapy, leading to discontinuation of study drug, and a subsequent antibiotic was started for treatment of pneumonia because the investigator considered the improvement insufficient.

Clinical Outcome Indeterminate

- If circumstances precluded classification as cure or failure, such as missing posttreatment information or early discontinuation of treatment for reasons that were not drug related.

  Or

- A new antibiotic was given for any reason other than CAP, bronchitis, any other lower RTI or an infection at another relevant site (e.g., meningitis, sepsis).

  Or

- An adverse event was present at or before pretherapy/entry (regardless of whether it worsened or not during treatment) and led to discontinuation of study drug, and a subsequent antibiotic was started for treatment of pneumonia.

  Or

- A laboratory measurement fulfilling an exclusion criterion was identified after starting study drug treatment and led to discontinuation of study drug (whether reported as an adverse event or not).

(M. O. Comment: Bacteriological outcome definitions were also substantially similar for studies 4003 and 3012 (and the CAP studies in the original NDA). The reviewer chose to focus on clinical outcome because the bacteriological outcome result for CAP is typically driven by the clinical outcome, including the need for further antibiotic treatment. The isolation or eradication of a pathogen rarely, if ever, determines the CAP clinical outcome without consideration of the presence or absence of clinical symptoms. The bacteriological outcome definitions that follow are from the final study report for study 4003.)

Bacteriological Outcome

Satisfactory If, at the posttherapy/TOC culture:

- The causative pathogen was absent **(eradication)**.

Or

- The subject had improved clinically to such an extent that a proper follow-up culture could not be obtained (no adequate sample for culture available because of clinical cure, no indication for an invasive procedure to obtain an appropriate sample) **(presumed eradication)**.

Or

- A bacterial strain other than the primary causative pathogen was isolated and subject had no signs or symptoms of active infection **(colonization)**.

Unsatisfactory If, at the posttherapy/TOC culture:

- The causative pathogen was still present, whether or not signs of infection were present **(persistence)**.

Or

- The causative pretherapy/entry pathogen was assumed to have persisted because a new antibacterial therapy was started for CAP, bronchitis, any other lower RTI or an infection at any relevant site that could indicate a complication of CAP (e.g., meningitis, sepsis) or the subject died due to one of these reasons and no sample was available **(presumed persistence)**.

Or

- 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 and laboratory evidence of pneumonia, and a new systemic anti-infective treatment (antibacterials, antifungals) was prescribed for CAP, any other lower RTI or an infection at any relevant site that could indicate a complication of CAP (e.g., meningitis, sepsis) **(superinfection)**.

Or

- Elimination of the initial infecting organism was 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 **(eradication and reinfection)**.

Or

- Reappearance of the causative pretherapy/entry pathogen after eradication from the original site of infection **(recurrence)**.

Indeterminate If it was not possible to categorize the microbiological response because of:

- Death not due to CAP, any other lower RTI or an infection at any relevant site that could have indicated a complication of CAP (e.g., meningitis, sepsis) and the lack of opportunity to perform further cultures.

Or

- Withdrawal of the subject from the study before follow-up cultures could be obtained.

Or

- Incomplete microbiological data.

Or

- Concurrent treatment of the subject with a potentially effective anti-infective agent that was not provided for CAP, any other lower RTI or an infection at any relevant site that could indicate a complication of CAP (e.g., meningitis, sepsis), not a superinfection, not a recurrence.

Or

- Adverse event(s) (other than conditions mentioned above) occurring on therapy, leading to discontinuation of study drug and subsequent antibiotic for the treatment of pneumonia.

Or

- Adverse event(s) present already at or before baseline (whether worsened or not on treatment) and leading to discontinuation of study drug with subsequent antibiotic for treatment of pneumonia.

Or

- Pretherapy/entry laboratory exclusion criteria known after starting study drug treatment and leading to discontinuation (whether reported as adverse event or not).

Appendix B: Study Synopsis of the new Japanese Study

HMR3647A/3107
Study Title: Investigation of the Efficacy and Safety of HMR3647 600 mg (q.d.) and Levofloxacin 300 mg (100 mg t.i.d.) against Community-acquired Pneumonia (Double-blind, Randomized, Drug-controlled, Non-inferiority Comparative Study)

Primary Objective: To investigate the clinical efficacy of HMR3647 against community-acquired pneumonia in a double-blind, randomized, non-inferiority comparative study, using levofloxacin (LVFX) as the comparator. To investigate the safety of HMR3647 using LVFX as the comparator
Secondary Objective: To investigate the bacteriological efficacy of HMR3647 using LVFX as the comparator

Study Design: Multicenter, double-blind, randomized, drug-controlled, two-group parallel-group, non-inferiority comparative study. The study began on December 7, 2000 and ended on June 21, 2001.
The patients were examined on the first day of treatment, 3 days later, and 7 days later or upon completion or discontinuation of treatment. During those examinations, they were observed for symptoms and signs, and given clinical laboratory tests. The patients also were observed a final time (14 to 28 days after initiation of study medication treatment, the final observation day).
This study was designed to investigate cases of community-acquired pneumonia that were presumed to be caused by common bacteria, or by *Mycoplasma pneumoniae*, *Chlamydophila (Chlamydia) pneumoniae*, or *Legionella pneumophila* strains (including bacterial pneumonia, atypical pneumonia, mycoplasmal pneumonia, chlamydial pneumonia, and Legionella pneumonia). Patients also had to satisfy the following criteria.

Criteria for use as evaluation subject
Must satisfy criteria 1 and 2, and at least 2 of the other 4 criteria (criteria 3 to 6)

1. It is a case in which an acute and new infiltrate shadow has been found by chest radiography, computed tomography (CT) of the chest, or other imaging technique.
2. It is a case in which some hematological sign of acute inflammation such as leukocytosis, neutrophilia, a 10% or greater shift to the left in the band cell count, increased CRP (.... 1.0 mg/dL), or accelerated erythrocyte sedimentation rate (ESR) has been observed.
3. It is a case in which there is fever (> 37°C)
4. It is a case in which there are respiratory symptoms such as coughing, sputum (purulent sputum), chest pain, and dyspnea.
5. It is a case in which there are moist rales.
6. It is a case in which the putative causative microorganisms have been identified in the sputum or other clinical sample, or a good quality sample can be obtained and it is highly likely that such microorganisms will be identified in that sample.

(M. O. Comment: Blood cultures were not performed in this study.)

Patient from 16 to 80 years of age could be enrolled. Females had to meet specific criteria to prevent study drug administration to pregnant women. Criteria for being classified as a mild or moderate pneumonia were included in the selection criteria as described in the following table:

Parameter	Severity of pneumonia infection		
	Mild (Meets at least 3 of the following 4 criteria)	**Moderate**	**Severe (Meets at least 3 of the following 4 criteria)**
Body temperature	<37.5°C	Neither mild nor Severe	≥38.6°C
Chest x-ray shadow score	<4 points		≥6 points
WBC count	<10,000/mm^3		≥20,000/mm^3
CRP	<10.0 mg/dL		≥20 mg/dL

Treatment:

1. HMR group: The patients in the HMR group were administered two 300 mg (titer) HMR3647 tablets (a total daily dose of 600 mg) once a day (q.d.), orally, after breakfast, for 7 days. Patients also received LVFX placebo.

(M. O. Comment: This daily dose is different, though lower than the one used in western studies. The applicant claims that this dose in Japanese patients provides similar drug exposure to the 800-mg dose in western populations.)

2. LVFX group: The patients in the LVFX group were administered one 100 mg (titer) LVFX tablet 3 times a day (t.i.d., total daily dose of 300 mg), orally, after each meal, for 7 days. Patients also received HMR 3647 placebo.

Efficacy data:

Clinical efficacy (at end of treatment): According to Japanese guidelines, "end of treatment" is defined as 7 days after initiation of study treatment. The clinical efficacy of the study medications at the end of the treatment was judged according to the following clinical efficacy evaluation criteria by comparing each patient's symptoms and signs before treatment and at the end of the treatment; and the efficacy rate was calculated.

Efficacy rate: Percent of all the patients in the analysis (minus those in whom the evaluation is "indeterminate") in whom the evaluation is "effective".

Analysis	Effective (At least 3 of the following 4 criteria are met)	Not effective	Indeterminate
Body temperature	Reduced to <37°C	The criteria for being judged "effective" are not met.	None of these parameters can be evaluated.
Chest x-ray shadow score	Reduced to 70% of baseline value or lower		
WBC count	Reduced to < 9,000/mm^3		
CRP	Reduced to 30% of baseline value or lower		

The study medication was judged "effective" when at least 3 of the 4 criteria listed above were met, and when only 3 of these criteria were met but no aggravation of the 4th parameter had occurred.

Clinical efficacy (at test of cure): As defined in the statistical analysis plan, the time window for "test of cure" was set at 14 to 28 days after initiation of study treatment, which provided a comparable time window to the 17 to 24-day time window used for test of cure in foreign studies. The test of cure was done according to the following criteria by comparing each patient's symptoms and signs before treatment and on the final observation day, and the clinical cure rate was calculated.

Clinical cure rate: Percent of the patients in the analysis (minus those in whom the evaluation is "indeterminate") in whom the evaluation is "cure".

Outcome	Criteria for evaluation in test of cure
Cure	When the symptoms and signs were found to have disappeared or improved, and no supplementary antimicrobial agent had been administered (systemically) to treat the underlying disease at test of cure
Failure	When the symptoms and signs were not found to have improved; or When the symptoms and signs were found to have disappeared or improved, but a supplementary antimicrobial agent had been administered (systemically) to treat the underlying disease at test of cure
Uncertain	When it was not possible to observe the symptoms and signs because the patient did not keep the appointment for the final observation
Indeterminate	When the symptoms and signs were found to have disappeared or improved, but an antimicrobial agent other than the study medications had been administered (systemically) to treat a condition other than the underlying disease at test of cure

The evaluation at test of cure was done in the cases in which the patients could not be observed on the final observation day. In those cases, that evaluation was influenced by whether or not the patients had received an antibiotic for their underlying disease after the study medication treatment and the clinical efficacy at end of treatment was evaluated.

(M. O. Comment: There are several significant differences between this study and the western studies submitted to the FDA in support of the application for CAP. Some of the differences related to study design such as the inclusion/exclusion criteria, microbiological testing, methods for assessing outcome at the EOT, and dose of study medication. Other important differences related to data collection, the recorded information for individual patients, and limited access to information for non-DRSP cases. The applicant provided narratives for the patients with CAP due to DRSP in the equivalent of a per-protocol population, but the reviewer had no means to independently confirm that all patients with DRSP were identified.

These differences are important because they limit the ability of the reviewer to independently assess the diagnosis and outcome of CAP. For example, the chest X-ray score was not clearly described in the protocol or supporting materials. Therefore, the reviewer was unclear as to the meaning of a particular score. The patient narratives did not include descriptions of the radiologic results. The reviewer had no means to assess the adequacy of radiologic diagnosis. Also, the clinical signs and symptoms recorded in the patient narratives and CRF's are not as extensive, limiting the reviewer's ability to independently assess the clinical diagnosis of CAP. Another example shows the impact of the methods for assessing outcome. Since the Japanese trials are designed for primary outcome analysis at

EOT, the WBC, CRP, fever, and CXR score drove the use of other antibiotics. Ultimately, this determined the outcome of cure or failure at the later TOC visit. However, the reviewer is unable to determine how well the changes in the EOT criteria correlate with improvement in clinical signs and symptoms. The limited information on clinical signs and symptoms recorded do not allow the reviewer to independently assess the outcomes of cure or failure. These differences limited the comparability of Western cases of CAP due to DRSP to the Japanese cases identified by the applicant.

The reviewer concluded that the Japanese data could be used as supportive evidence for the applicant's DRSP claims in CAP. However, the reviewer considered it inappropriate to combine the clinical cases from Western studies with those from Japanese studies.

, since the reviewer was limited in his ability to independently assess the diagnosis and outcome in these CAP patients. The data from cases in Japanese study 2105 faced similar limitations and were also treated as supportive.)

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Appendix C: Telithromycin Narratives – Drug Resistant S. pneumoniae

Telithromycin – Failures or Indeterminate Outcomes
Study 3000
3000/101/1365

— is an 18 y/o previously healthy male non-smoker from Argentina enrolled in study 3000 on 9/15/1998 for pneumonia. The patient was noted with moderate chills, cough, dyspnea, and pleuritic chest pain of one day's duration. Sputum production was recorded as mild. Vital signs included an axillary temperature of 38 °C and respiratory rate of 24. Rales and bronchial breath sounds were present on auscultation. Edema of the extremities was the only other physical finding noted. Laboratory studies included an elevated WBC count (26,200/mm^3) with a predominance of neutrophils (86% Seg., 5% Bands), an ESR = 78 mm/hr, and a CRP = 49.6. Baseline BUN and creatinine were also elevated at 112/1.56. Chest X-ray was reported with L segmental consolidation of a single lobe and an "alveolar picture". Blood and sputum samples grew *S. pneumoniae* resistant to penicillins only. The investigator characterized his infection as moderate. His next visit was on 9/22/98, at which time he had mild cough, dyspnea and sputum production. PE indicated the presence of rales. He was afebrile, unable to produce sputum, and had blood taken for culture (result = no growth). The study medication was stopped and he was started on penicillin 6 million unit oral tablets (regimen unknown) for another 2-3 days. He had taken 6 doses of telithromycin over 7 days. The investigator indicated that the patient met exclusion criteria for the study (increased BUN, creatinine and INR), but could not be reached until he showed up on the 22nd. Repeat laboratories on 9/25/98 showed normal BUN, creatinine and INR. ALT had risen to 55 IU/L. The patient was categorized as having an indeterminate outcome. Later follow-up after treatment with penicillin showed resolution of all signs and symptoms on 10/1/98. The only adverse event was eosinophilia, noted at this follow-up visit.

(M. O. Comment: After 6 days of Ketek treatment, the patient appears to have improved, although the penicillin treatment does not allow a clear determination of treatment effect. The investigator's assessment is equally confused in the CRF, with the patient marked as "improved", then "not improved sufficiently and antibiotics started", then indeterminate. The notes indicate that antibiotic treatment was changed because of abnormal baseline labs, but it seems unusual that the investigator would not repeat these lab tests when he was getting a blood culture. The patient is appropriately categorized as non-evaluable with an indeterminate outcome. In a more conservative analysis, the patient could be considered a non-evaluable treatment failure because other antibiotics were started for the treatment of the baseline infection.)

3000/605/1091

— is a 78 y/o female non-smoker enrolled on 2/4/99. Her past medical history includes hypertension, deafness, anxiety, GE reflux, and unspecified nutritional deficiencies. Baseline symptoms included severe cough and moderate sputum production. Chills, dyspnea, and pleuritic chest pain were all of mild intensity. Her vital

signs included a respiratory rate of 20/minute and a rectal temperature of 36.8 °C (T_{max} on the day before enrollment was recorded as 38.6 °C). Rales and dullness to percussion were noted on PE. Frontal CXR showed left-sided multilobar consolidation. Her WBC count was 11,400 cells/mm^3 (89% Neutrophils), and a normal ESR. Her arterial blood gas included a pO_2 of 55 mmHg with a normal pH. Sputum Gram stain showed >25 PMN and 10-25 epithelial cells with Gram-negative cocci and Gram-positive bacteria other than diplococci. Sputum culture collected by BAL indicated the presence of *S. pneumoniae* (10^5 CFU/mL, penicillin and erythromycin resistant), *H. influenzae* (10^5 CFU/mL), and *M. catarrhalis* (10^3 CFU/mL). *S. pneumoniae* resistant to penicillin and intermediate to erythromycin was also isolated from blood cultures.
At the on-therapy visit on 2/8/99, the symptoms of infection had improved with moderate cough, mild dyspnea and mild sputum production as the remaining symptoms. Her PE was unchanged and her respiratory rate was 18/min. She was afebrile. Sputum Gram stain showed >25 PMN and 10-25 epithelial cells with Gram-negative bacilli, and sputum culture results at this visit grew 10^3 CFU/mL of Citrobacter freundii. Repeat blood cultures were not recorded for this visit. She completed 10 days of telithromycin on 2/13/99.
At EOT on 2/15/99, she had mild cough and dyspnea as remaining symptoms. Her PE indicated that rales and dullness to percussion were now absent, but vital signs included a fever of 38.8 °C. A blood culture at this visit showed no growth. A urine culture performed at this visit grew S. aureus ($\geq 10^7$ CFU/mL). Clinical response was recorded as improved at this visit. However, the AE reports for this patient indicated that she was readmitted to the hospital on 2/18/99 for suspicion of a pulmonary embolism or lower respiratory reinfection. Her signs/symptoms included nocturnal dyspnea, chest pain, tachycardia and fever. She was started on IV piperacillin and amikacin with vancomycin added the next day. She continued on IV antibiotics until 2/23/99, then switched to oral pristinamycin until 3/1/99 when ofloxacin was started. At the TOC visit on 2/26/99, all pneumonia-related signs and symptoms were recorded as absent. The assessment was recorded as failure with antibiotics added for the disease under investigation.

(M. O. Comment: The urine culture results appear to be a confounding factor in the determination of this patient's outcome. However, enough of the recorded information in the CRF points to worsening of respiratory infection as the reason for treatment. The patient was appropriately assessed as an evaluable treatment failure by the applicant.)

Study 3001
3001/0111/010
~ is a 66 y/o male non-smoker enrolled on 11/20/98. His past history includes aortic stenosis, coronary artery disease, and saphenectomy. All symptoms were present and recorded as mild. Sputum was mucopurulent. T=38.8 axillary and RR=22 breaths/min. Rales and dullness to percussion were noted on exam. A right lower lobe infiltrate was noted on CXR. The infection was categorized as moderate in severity. Sputum Gram stain had >25 PMN and <10 epithelial cells with Gram-positive diplococci and Gram-negative cocci. Blood and sputum culture results indicate growth of penicillin-resistant *S. pneumoniae*. At the on-therapy visit on 11/23/02, mild cough and sputum production

were recorded as present. He was afebrile. PE findings were the same. Blood culture results were negative. However, the patient experienced nausea, "sea sickness", and "inestability" to walk after taking study medication. These symptoms continued on the next day, along with dyspnea, hypotension, and tachycardia. ECG results noted sinus tachycardia with ventricular and supraventricular asystole, similar to the baseline ECG. However, the QTc had increased from 379 to 462 msec. Given the results of the baseline blood culture, the investigator elected to discontinue the study medication. The patient was treated with ceftriaxone for 5 days. The symptoms and signs of pneumonia were absent at the subsequent visits. The investigator categorized the patient's outcome as indeterminate.

(M. O. Comment: The investigator sited the baseline blood culture results in deciding to start ceftriaxone. Although the investigator categorized the outcome as indeterminate, the M. O. considers the patient a failure in the setting of this double-blind randomized trial. Both the adverse events and the concerns that oral treatment was inadequate played a role in the decision to change treatment.)

3001/0902/002

— is a 39 y/o male smoker, enrolled on 8/28/98. His oral temperature was 38.8 C and his respiratory rate was 44 breaths/min. Most baseline symptoms were categorized as moderate or severe. Only dullness to percussion was noted on exam. Consolidation of a single lobe on the left side was noted on CXR. The current infection was categorized as moderate by the investigator. Sputum Gram stain was noted with >25 PMN, >25 epithelial cells, and mixed flora. Sputum culture grew *S. pneumoniae* resistant to penicillin and erythromycin. Blood cultures showed no growth. The patient appeared to improve at the on-therapy and EOT visits, but there was a recurrence of fever and symptoms of infection prior to the TOC visit. The patient was categorized as a failure and started on cefuroxime and erythromycin. H. influenzae susceptible to amoxicillin was isolated from sputum cultures at the EOT and TOC visits. The patient improved after treatment with cefuroxime and erythromycin.

(M. O. Comment: Respiratory rate >30/min. was one of the exclusion criteria, but not noted as such until the third day of treatment. The patient also received a single dose of IV "amoxycillin" just prior to enrollment. These protocol violations were noted, but the patient was continued on the study. The patient should be categorized as a failure.)

3001/1002/027

— is a 77 y/o female enrolled on 9/14/98. Her past history included squamous cell carcinoma, chronic obstructive pulmonary disease, and coronary artery disease. Presenting symptoms included moderate cough, dyspnea, chest pain, and sputum production. Mild chills were also noted. Her oral temperature was 38.1 C and his respiratory rate was 20/min. Her heart rate was 140 and her blood pressure was 95/70. Moderate rales and rhonchi were noted on PE. Dullness to percussion, bronchial breath sounds, wheezing, and egophony were categorized as mild. Right-sided consolidation of a single lobe was reported on CXR. Sputum Gram stain was noted with >25 PMN, >25

epithelial cells, Gram-positive bacteria (other than diplococci) and Gram-negative bacilli. Sputum culture grew 3+ *H. influenzae*, 2+ *S. pneumoniae* resistant to penicillin and erythromycin, and 2+ *S. aureus*. Blood cultures showed no growth. By the on-therapy visit on 9/16/98, the patient had begun on IV therapy with gentamicin and ceftriaxone for lack of clinical improvement. The patient died at — on — of circulatory, kidney, and respiratory failure.

(M. O. Comment: This patient was considered an evaluable failure by the applicant and the reviewer. My assessment of her Fine score was 3 based on available information. The ISE narrative indicates that this patient should have been treated with IV antibiotics siting her low blood pressure, but this assessment was made retrospectively. The protocol excluded patients with SBP <90 and DSP <60. At the initial visit, the investigator categorized her infection as moderate.)

Study 3009OL
3009OL/0369/105

— is a 37 y/o female non-smoker enrolled on 9/07/99. Her baseline symptoms included moderate cough, chills, chest pain, and tachypnea. Mild sputum production (mucoid) and dyspnea were also reported. Her vital signs included an oral temperature of 39.2 °C and a respiratory rate of 28/min. Moderate rales and dullness to percussion were noted on PE. CXR showed dense changes in the posterior segment of the right lower lobe as well as some adjacent segments. Bronchial wall thickening and infiltrates around the hilum were also noted. The infection was categorized as moderate. The sputum culture grew 3+ *S. pneumoniae*. The blood culture also grew *S. pneumoniae* resistant to penicillin and erythromycin. At the on-therapy visit on 9/10/99, the same symptoms and signs were present. The patient's oral temperature was 37.2 °C. Overall, the patient was categorized as unchanged at this visit. The blood culture obtained at this visit grew *S. pneumoniae* resistant to penicillin and erythromycin. Telithromycin was stopped and the patient was treated with IV penicillin and IV cefoxitin. The patient was improving on these IV antibiotics at a visit on 9/15/99. The withdrawal page indicated that the patient recovered on non-trial antibiotics.

(M. O. Comment: This case is particularly concerning because of the presence and persistence of bacteremia in a patient who otherwise appeared to have moderate infection. The patient was categorized as Fine class 1. The patient was considered an evaluable failure by the applicant.)

Study 3010
3010/0473/009

— is a 77 y/o male smoker enrolled on 7/31/2000. His past medical history included COPD, CHF, CAD, CVD, and renal disease. He had a past history of cancer from 15 years prior to enrollment. Baseline symptoms included mild cough, chills, chest pain, and moderate dyspnea. There was also moderate production of purulent sputum. Vital signs included an oral temperature of 98.6 °F and a respiratory rate of 16/min. Moderate rhonchi, mild rales and mild dullness to percussion were noted on PE. CXR showed a right lower lobe parenchymal infiltrate. The infection was categorized as moderate.

Sputum culture results included *S. pneumoniae* resistant to penicillin and erythromycin. *H. influenzae* and *M. catarrhalis* also grew from the sputum culture. The on-therapy visit on 8/02/00, moderate cough, chest pain, and dyspnea remained. Vital signs included a respiratory rate of 18/min. and an oral temperature of 99.0 °F. Mild rales and rhonchi were present on PE. The patient was considered improved at this visit. However, the patient had been experiencing multiple adverse events, including nausea, vomiting, abdominal discomfort from constipation, and worsening ankle edema from his renal insufficiency. On the 5th day of telithromycin treatment, the patient was found by the nursing staff with labored respirations. ABG results included a pH=7.08, pO2=68 and PCO2=68. He was transferred to the ICU, but went into cardiac arrest. On intubation, copious watery/blood-tinged secretions were noted. Attempts at resuscitation were unsuccessful and the patient died.

(M. O. Comment: The investigator suspected acute aspiration as the cause of the sudden worsening. The investigator completed an end-of therapy assessment sheet, initially indicating the subject developed new clinical findings consistent with active infection. This assessment was later changed to an indeterminate outcome. In my opinion, the sudden worsening has several possible explanations, including decompensation of his CHF or sudden worsening of infection/sepsis. The respiratory arrest on antibiotic treatment should be considered a failure.)

Study 3012
3012/1041/003
—, is a 78 y/o female, enrolled on 12/19/2001. She had a history of COPD. Baseline symptoms included mild cough, dyspnea, and sputum production (purulent). Moderate tachypnea, moderate chills, and severe chest pain were also noted. Her oral temperature was 97.4 °F and her respiratory rate was 26/min. Moderate rales, mild egophony, and mild bronchial breath sounds were noted on PE. CXR findings were noted as "COPD with bibasilar atelectasis – can't exclude pneumonia especially L lung base". The infection was categorized as moderate. Sputum Gram stain showed >25 PMN, <10 epithelial cells, Gram-positive diplococci, Gram-negative bacilli and cocci. Sputum culture grew 4+ *S. pneumoniae*, 4+ *M. catarrhalis*, and 1+ *H. parainfluenzae*. The *S. pneumoniae* isolate was resistant to erythromycin. At the on-therapy visit on 12/21/01, Mild cough, dyspnea, and tachypnea were the remaining symptoms. Her respiratory rate was 24/min. Moderate rales were noted on PE. The patient completed 7 days of telithromycin. At the EOT visit on 12/26/01, mild tachypnea and mild rales were the only remaining findings. The patient was considered improved. Worsening pneumonia was noted as an adverse event starting on — Elevated temperature and L basilar infiltrate were listed on the adverse event form. A CXR was reported with an infiltrate at the L lung base, including the lingula and the retrocardiac region. The CXR was considered worsened in comparison to the baseline CXR. The patient was hospitalized and started on levofloxacin. Other medication for COPD and diabetes were also given. At the TOC visit on 1/7/02, mild chest pain and moderate dyspnea were the only reported symptoms. Moderate rales and mild wheezing were present on PE. The patient was categorized as a failure, requiring a new antibiotic for an adverse event.

(M. O. Comment: This case represents a recurrence of pneumonia between the EOT and TOC visits. She was categorized as an evaluable failure by the applicant.)

3012/3019/001

— is an 82 y/o female non-smoker, enrolled on 01/02/02.At baseline, she reported moderate cough, dyspnea, and tachypnea with mild sputum production (mucopurulent). Severe chest pain and chills were also noted. Her vital signs included a tympanic temperature of 38.5 °C and a respiratory rate of 26/min. Moderate rales and mild dullness to percussion were noted on PE. A CXR showed "pneumopathy" of the left base. The infection was categorized as moderate. According to the CRF, the blood culture from the day prior to enrollment grew *S. pneumoniae* resistant to penicillin and erythromycin, although the repeat blood culture on the day of enrollment showed no growth. The patient did receive amoxicillin/clavulanate on the day prior to enrollment, which was stopped for an allergic rash. No pathogens were reported from the sputum culture. An on-therapy visit was reported on 1/4/02, or possibly 1/6/02. Mild cough, dyspnea, tachypnea, and mucoid sputum production were noted. Chest pain was moderate. The patient was afebrile and her respiratory rate was 20/min. Mild rales and dullness to percussion were reported on PE. The patient was considered improved. There was no growth from a blood culture. The patient completed 7 days of telithromycin. An early withdrawal visit occurred on 1/10/02. Mild chest pain, cough, dyspnea, and mucoid sputum production were noted. Her vital signs included a tympanic temperature of 37.0 C and a respiratory rate of 16/min. Mild rales were noted on PE. A normal CXR was reported. The patient received ceftriaxone from 1/11/02 through 1/19/02 for "treatment failure" and "clinical failure of pneumopathy", according to the completion of study CRF page. However, these comments were later crossed out. Sputum Gram stain was not performed though a culture was reported with *H. parainfluenzae*. The outcome for the last visit was initially marked as failure (New antibiotic required in the following specific indirect situations associated with insufficient improvement: adverse event). The adverse event forms indicate the patient had bronchitis, with cough, fever, rhinitis, and diffuse rhonchi. The outcome was later changed to indeterminate.

(M. O. Comment: The case report clearly indicates that the patient was started on other antibiotics for a respiratory tract infection shortly following the end of study drug. The patient was appropriately categorized as non-evaluable, given the culture results after prior antibiotic treatment. However, it is reasonable to consider the *S. pneumoniae* isolated from blood on the day prior to enrollment as the causative pathogen.)

3012/4003/022

— is a 43 y/o male smoker, enrolled on 9/10/2001. Baseline symptoms included moderate cough, chest pain, and sputum production (mucopurulent). Chills, dyspnea and tachypnea were mild. His vital signs included an oral temperature of 38.2 °C, and a respiratory rate of 22/min. Moderate rales, rhonchi, and dullness to percussion were noted on PE. A urinary antigen test for *S. pneumoniae* was positive. The CXR was noted with dense consolidation on the RML and increased markings in the left perihilar region and left lower lobe. The infection was categorized as moderate. Sputum Gram stain was