CAP CLINICAL RESISTANT MIC DATA

Protocols #3000, #3001, #3010, and #3012

TABLE 37* CAP: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/mL) or erythromycin resistant (MIC ≥ 1 µg/mL) without centers excluded by FDA - **bmITT** not PPb population.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome[c]	Bacteriological Outcome
Study #3000					
PRSP (n = 1)	1[b]	0.015	---	1 = Indeterminate	1 = Indeterminate
ery-R (n = 1)	1	0.030	*erm*B	1 = Cure	1 = Presumed Eradication
Study #3001					
PRSP (n=2)	1[b]	0.015	---	1 = Indeterminate	1 = Indeterminate
	1	0.015	---	1 = Failure	1 = Eradication
Study #3010					
PRSP (n=1)	1	0.030	---	1 = Cure	1 = Presumed Eradication
ery-R (n =1)	1	0.030	*erm*B	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 1)	1	2.000	*mef*E	1 = Indeterminate	1 = Indeterminate
Study #3012					
ery-R (n = 1)	1	0.250	ermB	1 = Indeterminate	1 = Indeterminate
PRSP / ery-R (n = 4)	1	0.060	*erm*B	1 = Cure	1 = Presumed Eradication
	1	0.060	*erm*B	1 = Indeterminate	1 = Indeterminate
	1	1.000	*erm*B / mefE	1 = Cure	1 = Presumed Eradication
	1	0.500	*erm*B / mefE	1 = Failure	1 = Recurrence

* Adapted from NDA 21-144, Electronic Mail, Dated 09/12/02, First Attachment, Page 1.

[a] Teli = telithromycin
[b] Sample Source = blood
[c] Clinical Response = Cure, Failure, or Indeterminate

n = total number of isolates.

TABLE 38* CAP: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/mL) or erythromycin resistant (MIC ≥ 1 µg/mL) without centers excluded by FDA - **bmITT** not PPb population.

Combined Summary Resistance MIC Analyses

Protocols #3000, #3001, #3010, and #3012

Resistance	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome[c]	Bacteriological Outcome
PRSP	2[b]	0.015	---	1 = Indeterminate	1 = Indeterminate
(n = 4)	1	0.015	---	1 = Failure	1 = Eradication
	1	0.030	---	1 = Cure	1 = Presumed Eradication
ery-R	1	0.250	ermB	1 = Indeterminate	1 = Indeterminate
(n = 3)	2	0.030	*erm*B	1 = Cure	1 = Presumed Eradication
PRSP / ery-R	1	0.060	*erm*B	1 = Cure	1 = Presumed Eradication
(n = 5)	1	0.060	*erm*B	1 = Indeterminate	1 = Indeterminate
	1	0.500	*erm*B / mefE	1 = Failure	1 = Recurrence
	1	1.000	*erm*B / mefE	1 = Cure	1 = Presumed Eradication
	1	2.000	*mef*E	1 = Indeterminate	1 = Indeterminate

* Adapted from NDA 21-144, Electronic Mail, Dated 09/12/02, First Attachment, Page 1..

[a] Teli = telithromycin
[b] Sample Source = blood
[c] Clinical Response = Cure, Failure, or Indeterminate

n = total number of isolates.

Summary:

If the *Streptococcus pneumoniae* isolate contained the *erm*B genotype, the MIC is higher. The "Failures" and the "Indeterminate" results obscure any favorable conclusions on the activity of telithromycin in this bmITT population.

TABLE 39[*] Shows the CAP clinical studies with *Streptococcus pneumoniae* Erythromycin-Resistant (Ery-R) strains with genotype *mef*A and/or *erm*B.

Genotype	Telithromycin MIC (µg/mL)	N	Eradicated/ Presumed Eradicated (%)
Ery-R *mef*(A) Only	0.03	1	1 (100)
	0.06	5	5 (100)
	0.12	8	6 (75.0)
	1.0	4	4 (100)
	Total	**18**	**16 (88.9)**
Ery-R *erm*(B) Only	0.016	2	2 (100)
	0.03	11	8 (72.7)
	0.06	5	4 (80)
	0.12	4	4 (100)
	0.25	3	3 (100)
	0.5	2	2 (100)
	1.0	1	1 (100)
	Total	**28**	**24 (85.7)**
Ery-R *mef*(A)/*erm*(B)	0.12	1	1 (100)
	0.5	2	2 (100)
	Total	**3**	**3 (100)**

[*] Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, on Page 101.

mef(A) = resistant to macrolides based on drug efflux.

erm(B) = resistant to macrolides based on methylation of 23S rRNA.

mef(A) / *erm*(B) = resistant to macrolides based on both genotypes.

Telithromycin against *Streptococcus pneumoniae* erythromycin-resistant aforementioned genotype strains:

Ery-R *mef*A Only: $MIC_{88.9} \leq 0.12$ µg/mL (14/18)

Ery-R *erm*B Only: $MIC_{89.3} \leq 0.25$ µg/mL (25/28)

Ery-R *mef*A / *erm*B: $MIC_{100} \leq 0.5$ µg/mL (3/3)

The telithromycin MICs are very low when *Streptococcus pneumoniae* isolates contain only 1-phenotype (either *mef*A or *erm*B). Only the bacteriological response is provided (i.e., eradicated and presumed eradicated).

Protocols #3000, #3001, #3006, #3009, #3010, #3013 & #3014

TABLE 40* CAP: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/mL) or erythromycin resistant (MIC >= 1 µg/mL) without centers excluded by FDA - **PP_b** population.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #3000					
PRSP (n = 2)	1[b]	0.15	---	1 = Cure	1 = Eradication
	1	0.15	---	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 1)	1[b]	0.30	*erm*B	1 = Failure	1 = Presumed Eradication
Study #3001					
PRSP / ery-R (n = 3)	1[b]	0.30	*erm*B	1 = Cure	1 = Presumed Persistence
	1	0.30	*erm*B	1 = Failure	1 = Presumed Persistence
	1	0.30	*erm*B	1 = Cure	1 = Presumed Persistence
Study #3006					
PRSP (n = 3)	1[b]	0.008	---	1 = Cure	1 = Eradication
	1	0.008	---	1 = Cure	1 = Presumed Eradication
	1	0.030	---	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 1)	1	0.30	*mef*E	1 = Cure	1 = Presumed Persistence
Study #3009					
PRSP (n = 1)	1[b]	0.030	---	1 = Cure	1 = Presumed Eradication
ery-R (n = 2)	1	0.030	*erm*B	1 = Cure	1 = Presumed Eradication
	1	1.000	*mef*E	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 2)	1[b]	0.060	*mef*E	1 = Cure	1 = Presumed Eradication
	1[b]	0.120	*mef*E	1 = Failure	1 = Presumed Persistence

TABLE 40* (con't) CAP: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC >= 2 µg/mL) or erythromycin resistant (MIC >= 1 µg/mL) without centers excluded by FDA - **PP_b** population.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #3010					
PRSP (n = 2)	2	0.030	---	2 = Cure	2 = Presumed Eradication
ery-R (n = 3)	1	0.030	*erm*B	1 = Cure	1 = Eradication
	1[b]	0.500	*mef*E	1 = Cure	1 = Presumed Eradication
	1[b]	1.000	*mef*E	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 4)	1	0.060	*mef*E	1 = Cure	1 = Presumed Eradication
	1	0.250	*erm*B	1 = Cure	1 = Presumed Eradication
	2	0.500	*erm*B / *mef*E	1 = Cure	1 = Presumed Eradication
Study #3012					
PRSP (n = 1)	1	0.008	---	1 = Cure	1 = Presumed Eradication
ery-R (n = 6)	1[b]	0.030	*erm*B	1 = Cure	1 = Eradication
	1[b]	0.120	*erm*B	1 = Cure	1 = Eradication
	1[b]	0.600	*mef*E	1 = Cure	1 = Eradication
	1	0.016	*erm*B	1 = Cure	1 = Presumed Eradication
	1	0.060	*erm*B	1 = Cure	1 = Presumed Eradication
	1	0.120	*mef*E	1 = Failure	1 = Presumed Eradication
PRSP / ery-R (n = 2)	1[b]	1.000	*erm*B	1 = Cure	1 = Presumed Eradication
	1	0.120	*mef*E	1 = Cure	1 = Presumed Eradication
Study #4003					
ery-R (n = 5)	1	0.060	*mef*E	1 = Cure	1 = Presumed Eradication
	1	0.120	*mef*E	1 = Cure	1 = Presumed Eradication
	1	1.000	*mef*E	1 = Cure	1 = Presumed Eradication
	1	0.030	*erm*A / *erm*B	1 = Cure	1 = Presumed Eradication
	1	0.500	*erm*A / *erm*B	1 = Cure	1 = Presumed Eradication

* Adapted from NDA 21-144, Electronic Mail, Dated 09/12/02, Second Attachment, Pages 1 to 2.
[a] Teli = telithromycin; [b] Sample Source = blood

n = total number of isolates.

TABLE 41* CAP: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC >= 2 µg/mL) or erythromycin resistant (MIC >= 1 µg/mL without centers excluded by FDA - **PP_b** population.

Combined Summary Resistance MIC Analyses (Protocols #3000, #3001, #3006, #3009, #3010, #3013 & #3014)

Resistance	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
PRSP (n = 9)	1[b]	0.008	---	1 = Cure	1 = Eradication
	2	0.008	---	2 = Cure	2 = Presumed Eradication
	1[b]	0.150	---	1 = Cure	1 = Eradication
	1	0.150	---	1 = Cure	1 = Presumed Eradication
	1[b]	0.030	---	1 = Cure	1 = Presumed Eradication
	3	0.030	---	3 = Cure	3 = Presumed Eradication
ery-R (n = 16)	1	0.016	*ermB*	1 = Cure	1 = Presumed Eradication
	1[b]	0.030	*ermB*	1 = Cure	1 = Eradication
	1	0.030	*ermB*	1 = Cure	1 = Eradication
	1	0.030	*ermB*	1 = Cure	1 = Presumed Eradication
	1	0.030	*ermA / ermB*	1 = Cure	1 = Presumed Eradication
	1	0.060	*ermB*	1 = Cure	1 = Presumed Eradication
	1[b]	0.060	*mefE*	1 = Cure	1 = Eradication
	1	0.060	*mefE*	1 = Cure	1 = Presumed Eradication
	1[b]	0.120	*ermB*	1 = Cure	1 = Eradication
	1	0.120	*mefE*	1 = Cure	1 = Presumed Eradication
	1	0.120	*mefE*	1 = Failure	1 = Presumed Eradication
	1[b]	0.500	*mefE*	1 = Cure	1 = Presumed Eradication
	1	0.500	*ermA / ermB*	1 = Cure	1 = Presumed Eradication
	1[b]	1.000	*mefE*	1 = Cure	1 = Presumed Eradication
	2	1.000	*mefE*	2 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 13)	1[b]	0.060	*mefE*	1 = Cure	1 = Presumed Eradication
	1	0.060	*mefE*	1 = Cure	1 = Presumed Eradication
	1[b]	0.300	*ermB*	1 = Cure	1 = Presumed Persistence
	1	0.300	*ermB*	1 = Cure	1 = Presumed Persistence
	1[b]	0.300	*ermB*	1 = Failure	1 = Presumed Eradication
	1	0.300	*ermB*	1 = Failure	1 = Presumed Persistence
	1	0.300	*mefE*	1 = Cure	1 = Presumed Persistence
	1[b]	0.120	*mefE*	1 = Failure	1 = Presumed Persistence
	1	0.120	*mefE*	1 = Cure	1 = Presumed Eradication
	1	0.250	*ermB*	1 = Cure	1 = Presumed Eradication
	2	0.500	*ermB / mefE*	2 = Cure	2 = Presumed Eradication
	1[b]	1.000	*ermB*	1 = Cure	1 = Presumed Eradication

* Adapted from NDA 21-144, Electronic Mail, Dated 09/12/02, Second Attachment, Pages 1 to 2.

[a] Teli = telithromycin
[b] Sample Source =blood

n = total number of isolates.

Summary:

Telithromycin has good activity against 9-PRSP in the MIC range = 0.008 to 0.030 µg/mL. The clinical outcome are all 9-Cures and the bacteriological outcomes are 2-Eradications and 7-Presumed Eradications.

Telithromycin has good activity against ery-R phenotype *Streptococcus pneumoniae* isolates in the MIC range = 0.016 to 1.0 µg/mL. The clinical outcome are 15-Cures and 1-Failure (*mef*E phenotype) and the bacteriological outcomes are 4-Eradications and 12-Presumed Eradications.

Telithromycin has fair activity PRSP / ery-R phenotype *Streptococcus pneumoniae* isolates in the MIC range = 0.060 to 1.000 µg/mL. The clinical outcomes are 10 Cures and 3-Failures (2-*erm*B & 1-*mef*E phenotypes) and the bacteriological outcomes are all 13-Presumed Eradications.

Of particular interest are the isolates having telithromycin MICs ≥ 1.0 µg/mL, the proposed susceptible breakpoint for *S. pneumoniae*. The microbiological evaluation of the bacteriological per protocol (PP_b) data suggests that of isolates with MICs of 1.0 µg/mL, all three clinical cases, including one bacteremia case, were clinical and bacteriological successes. Also presented were three cases with MICs of 0.5 µg/mL and these were also clinical and bacteriological successes.

CAP CLINICAL STUDIES - (JAPAN)

(Supportive Studies)

CAP Susceptibility Procedures

Validation of antimicrobial susceptibility testing methods and results for Japanese Studies #2105 and #3107 follow:

The Applicant stated that the isolates in Studies #2105 and #3107 were sent to the Clinical Microbiology Institute (CMI) in Portland, OR, USA. All isolates were re-identified and evaluated for susceptibility or resistance to telithromycin and erythromycin A. There were no category shifts [e.g., susceptibility (S) to resistance (R)] in the data from Japan as determined by CMI. CMI data were exclusively used in the clinical evaluation of response to treatment with telithromycin for these patients, and the results of the comparative susceptibility testing studies are included in the following described information:

CAP Clinical Protocol #2105

Japan Study #2105 is a double-blind, randomized, active 7-day telithromycin 600 mg q.d. and a 2-arm, parallel group 7-day telithromycin 800 mg q.d.

For more information refer to Dr. Fred Marsik's Clinical Microbiology Review #1 and #2, Dates Completed 11/30/00 and 05/11/01, respectively.

CAP Clinical Protocol #3107

Title:

Investigation of the Efficacy and Safety of HMR3647, telithromycin, 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).

Investigator(s), Study Site(s):

Indication: Community-acquired pneumonia.

Objectives:

-- Primary Objectives:

To investigate the clinical efficacy of HMR3647 against community-acquired pneumonia in a double-blind, randomized, non-inferiority comparative study, using levofloxacin (also know as LVFX) as the comparator; and

To investigate the safety of HMR3647 using levofloxacin as the comparator.

-- Secondary Objective:

To investigate the bacteriological efficacy of HMR3647 using levofloxacin as the comparator

Design:
This is a multicenter, double-blind, randomized, drug-controlled, two-groups parallel-group, non-inferiority comparative study

Population:
Patients 16 to 80 years of age with mild to moderate community-acquired pneumonia with clear symptoms of infection.

Treatments:

-- 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.

-- Levofloxacin group:

The patients in the levofloxacin 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.

TABLE 42. Criteria for Evaluation in Test of Cure*:

Outcome	Definition
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

* Adapted from EDR NDA 21-144, Dated 07/24/02, Clinical Study Rept. No. J2002CLN0001, p. 29

Bacteriological Efficacy Evaluation Criteria*:

The bacteriological efficacy of HMR3647 was evaluated at 7 days after initiation of study treatment (end of treatment). The evaluation was in accordance with the following criteria based on the results of microbiological assays performed before and after treatment.

TABLE 43* "explains the bacteriological outcomes, as follows:

Outcome	Definition
Eradication or presumed eradication	"Eradication" is the judgment to be given when the causative microorganism has disappeared from appropriately collected and incubated samples (such as purulent mucous plugs, purulent secretions, and purulent sputum) after administration of the study medication.
	"Presumed eradication" is the judgment to be given when the causative microorganism is presumed to have disappeared because suitable test samples (such as purulent mucous plugs, purulent secretions, and purulent sputum) can no longer be collected from the original infection focus as a result of the patient's response to the treatment.
Reduction or partial eradication	"Reduction" is the judgment to be given when a decrease in the amount of the original causative microorganism is confirmed; that is, when the amount of that microorganism is found quantitatively or semiquantitatively to have been reduced by at least 2 grades.* * (For example, from 10n to 10n-2 or from +++ to +)
	"Partial eradication" is the judgment to be given when the infection is caused by multiple causative microorganisms and some of those microorganisms have disappeared as a result of the treatment, regardless of the clinical efficacy of the treatment.
Microbial substitution (colonization)	"Microbial substitution (colonization)" is the judgment to be given when the original causative microorganism has disappeared as a result of the treatment, but another new potential causative microorganism unassociated with any definite symptom or sign of infection is detected where the original causative microorganism used to be.
Superinfection	"Superinfection" is the judgment to be given when the original causative microorganism has disappeared as a result of the treatment, but another new causative microorganism associated with a definite symptom and/or sign of infection is detected where the original causative microorganism used to be.
Persistence or recurrence (after temporary eradication)	"Persistence" is the judgment to be given when the original causative microorganism still is found in the infection focus after completion of the treatment whether or not there is any inflammation. This includes cases in which the amount of that microorganism is found quantitatively or semiquantitatively to have been reduced by 1 grade.
	"Recurrence" is the judgment to be given when the causative microorganism is proven to have disappeared from the infection site, but then is detected again in a sample collected from the same infection site after completion of the treatment.
Multiple infection	Sometimes, the original causative microorganism persists and a different new microorganism is detected during the treatment. "Multiple infection" is the judgment to be given when that phenomenon is associated with the persistence or aggravation of clinical or laboratory test findings of infection.
Indeterminate	This is the judgment to be given when none of the above-listed assessments can be given for various reasons.

* Adapted from EDR NDA 21-144, Dated 07/24/02, Clinical Study Rept. No. J2002CLN0001, p. 30

JAPANESE CAP CLINICAL RESISTANCE DATA

TABLE 44* shows the CAP (Japanese Studies #2105 and #3107): Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G and/or erythromycin A from single or mixed pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC

Subject (Study/Center/ Subject No.)	Age/ Fine Score	Isolate Source	MIC Susceptibility µg/mL			Geno-type	Bacterio-logical Outcome	Clinical Outcome
			TEL[a]	Pen G	Ery A			
Japanese studies, single *S. pneumoniae* isolates								
2105/30/30-4	75/NA	Sputum	0.016 (S)	1 (I)	8 (R)	*erm*(B)	Eradication	Cure
3107/120/105	68/NA	Sputum	0.03 (S)	0.06 (S)	256 (R)	*erm*(B)	Persistence or recurrence (after temporary erad)	Cure
2105/13/13-2[b]	27/NA	Sputum	0.03 (S)	2 (R)	>512 (R)	*erm*(B)	Pres erad	Cure
2105/30/30-2[b]	45/NA	Sputum	0.03 (S)	1 (I)	>512 (R)	*erm*(B)	Pres erad	Cure
3107/033/102	56/NA	Sputum	0.06 (S)	0.03 (S)	256 (R)	*erm*(B)	Erad or pres erad	Cure
3107/046/102[c]	27/NA	Sputum	0.06 (S)	0.03 (S)	256 (R)	*erm*(B)	Persistence[d]	Cure
2105/32/32-1	60/NA	Sputum	0.06 (S)	2 (R)	4 (R)	*mef*(A)	Pres erad	Cure
2105/46/46-1	29/NA	Sputum	0.06 (S)	2 (R)	>512 (R)	*erm*(B)	Eradication	Cure
3107/042/104	69/NA	Sputum	0.12 (S)	0.03 (S)	256 (R)	*erm*(B)	Erad or pres erad	Failure
3107/080/101[c]	65/NA	Sputum	0.12 (S)	0.03 (S)	256 (R)	*erm*(B)/ *mef*(A)	Erad or pres erad	Cure
2105/56/56-1	41/NA	Sputum	0.12 (S)	0.06 (S)	>512 (R)	*erm*(B)	Eradication	Cure
3107/002/110	73/NA	Sputum	0.12 (S)	2 (R)	8 (R)	*mef*(A)	Erad or pres erad	Cure
3107/013-102	75/NA	Sputum	0.12 (S)	0.03 (S)	16 (R)	*mef*(A)	Erad or pres erad	Cure
2105/17/17-1	40/NA	Sputum	0.25 (S)	0.03 (S)	>512 (R)	*erm*(B)	Pres erad	Cure
2105/15/15-1[b]	68/NA	Sputum	0.50 (S)	0.06 (S)	>512 (R)	*erm*(B)	Eradication	Failure
Japanese studies, mixed pathogen infections including *S. pneumoniae* isolates								
3107/077/103[e]	58/NA	Sputum	0.03 (S)	2 (R)	256 (R)	*erm*(B)	Erad[f]	Cure
2105/17/17-2	32/NA	Sputum	0.06 (S)	≤0.03 (S)	>512 (R)	*erm*(B)	Pres erad	Cure
3107/093/105	59/NA	Sputum	0.12 (S)	2 (R)	256 (R)	*erm*(B)	Erad or pres erad	Cure
3107/102/101	74/NA	Sputum	0.12 (S)	2 (R)	16 (R)	*mef*(A)	Erad or pres erad	Cure
3107/135/101	73/NA	Sputum	0.12 (S)	2 (R)	8 (R)	*mef*(A)	Erad[f]	Cure
3107/103/102[e]	70/NA	Sputum	0.25 (S)	0.03 (S)	256 (R)	*erm*(B)	Erad or pres erad	Cure

*Adapted from NDA 21-144. Electronic Mail, Dated 09/12/02.
Susceptibility: S = susceptible, I = intermediate, R = resistant. Fine score: NA = Not applicable, because the protocol did not capture all the criteria necessary for the Fine score.
Bacteriological outcome: Pres erad = presumed eradication, Pres persist = presumed persistence.
Genotyping for erythromycin A- (macrolide-)resistant isolates: NA = not applicable.
[a] Telithromycin susceptibility is based on the proposed breakpoint of 1 µg/mL
[b] Treated with 600 mg telithromycin (Study #2105); All other patients treated with 800 mg telithromycin (Study #2105).
[c] Antibiotic(s) that the investigators judged ineffective against the current infection had been taken for 3 days or longer prior to enrollment.
[d] Bacterial count decreased from +++ to + in semi-quantitative assay at the laboratory of study institution. This was categorized as "reduction or partial eradication" in CSR 3107 following Japanese procedures
[e] Antibiotic(s) that the investigators judged ineffective against the current infection had been taken for 3 days or longer prior to enrollment
[f] The *Streptococcus pneumoniae* isolates were eradicated.
*mef*A = resistant to macrolides based on drug efflux. *erm*B = resistant to macrolides based on methylation of 23S rRNA.
*mef*A / *erm*B = resistant to macrolides based on both genotypes.
Study #3107: Patients treated with 600 mg. telithromycin.

TABLE 45* CAP - Japanese Study – Protocol #2105: Subjects with *Streptococcus pneumoniae* isolates resistant to erythromycin A, with either *ermB*, *mefA*, or *ermB / mefA* genotypes, from single pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients (600 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB* genotype] = 3

Patients Cured = 2/3 (66.7%)	Eradication = 1/3 (33.3%)
Patients Failed = 1/3 (33.3%)	Presumed Eradication = 2/3 (66.7%)
	Eradication + Presumed Eradication = 3/3 (100%)

Number of patients (800 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB* genotype] = 4

Patients Cured = 4/4 (100%)	Eradication = 3/4 (75%)
	Presumed Eradication = 1/4 (25%)
	Eradication + Presumed Eradication = 4/4 (100%)

Number of patients (800 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *mefA* genotype] = 1

Patients Cured = 1/1 (100%)	Presumed Eradicated = 1/1 (100%)

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB / mefA* genotype] = None.

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients (600 mg and 800 treatment) isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB*, *mefA*, and *ermB / mefA* genotypes] = 8

Patients Cured = 7/8 (87.5%)	Eradication = 4/8 (50%)
Patients Failed = 1/8 (12.5%)	Presumed Eradicated = 4/8 (50%)
	Eradication + Presumed Eradication = 8/8 (100%)

TABLE 46* CAP - Japanese Study – Protocol #2105: Subjects with *Streptococcus pneumoniae* isolates resistant to erythromycin A, with *ermB*, *mefA*, or *ermB / mefA* genotypes, from mixed pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients (800 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB* genotype] = 1

Patients Cured = 1/1 (100%) Presumed Eradication = 1/1 (100%)

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with either *mefA* or *ermB / mefA* genotypes] = None.

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

TABLE 47* CAP - Japanese Study – Protocol #2105: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) from single pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients (600 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to penicillin (PRSP) = 1

Patients Cured = 1/1 (100%) Presumed Eradication = 1/1 (100%)

Number of patients (800 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to penicillin (PRSP) = 2

Patients Cured = 2/2 (100%) Eradication = 1/2 (50%)
Presumed Eradication = 1/2 (50%)
Eradication + Presumed Eradication = 2/2 (100%)

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients (600 mg and 800 treatment) isolated with *Streptococcus pneumoniae* isolates resistant to penicillin (PRSP) = 3

Patients Cured = 3/3 (100) Eradication = 1/3 (33.3%)
Presumed Eradicated = 2/3 (66.7%)
Eradication + Presumed Eradication = 3/3 (100%)

CAP - Japanese Study – Protocol #2105: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) from mixed pathogen infections by telithromycin MIC

susceptibility – **PP_b** population at post-therapy/TOC = None.

TABLE 48[*] CAP - Japanese Study – Protocol #2105: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A, with either *erm*B or *mef*A genotype, from single pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients (600 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *erm*B genotype] = 2

Patients Cured = 1/1 (100%) Presumed Eradication = 1/1 (100%)

Number of patients (800 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *erm*B genotype] = 2

Patients Cured = 1/1 (100%) Eradication = 1/1 (100%)

Number of patients (800 mg treatment) isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *mef*A genotype] = 1

Patients Cured = 1/1 (100%) Presumed Eradicated = 1/1 (100%)

[*] Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients (600 mg and 800 treatment) with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A with either *erm*B or *mef*A genotypes = 3

Patients Cured = 3/3 (100%) Eradication = 1/3 (33.3%)
Presumed Eradication = 2/3 (66.7%)
Eradication + Presumed Eradication total = 3/3 (100%)

CAP - Japanese Study – Protocol #2105: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with either *erm*B or *mef*A genotype] from mixed pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC = None.

TABLE 49* CAP - Japanese Study – Protocol #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to erythromycin A, with either *erm*B, *mef*A, or *erm*B / *mef*A genotypes, from single pathogen infections by telithromycin MIC susceptibility – PP_b population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome
Number of patients with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *erm*B genotype] = 4	
Patients Cured = 3/4 (75%) Patients Failed = 1/4 (25%)	Eradication or Presumed Eradication = 2/4 (50%) Persistence = 1/4 (25%) Persistence or Recurrence (after temporal eradication) = 1/4 (25%)
Number of patients with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *mef*A genotype] = 2	
Patients Cured = 2/2 (100%)	Eradication or Presumed Eradicated = 2/2 (100%)
Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *erm*B / *mef*A genotypes] = 1	
Patients Cured = 1/1 (100%)	Eradication or Presumed Eradicated = 1/1 (100%)

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients with *Streptococcus pneumoniae* isolates resistant to erythromycin A with *erm*B, *mef*A, or *erm*B / *mef*A genotypes = 7

Patients Cured = 6/7 (85.7%) Patients Failed = 1/7 (14.3%)	Eradication or Presumed Eradication = 5/7 (50%) Persistence = 1/4 (25%) Persistence or Recurrence (after temporal eradication) = 1/4 (25%)

TABLE 50* CAP - Japanese Study – Protocol #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to erythromycin A, with either *ermB*, *mefA* or *ermB / mefA* genotypes, from mixed pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB* genotype] = 3

Patients Cured = 3/3 (100%) Eradication = 2/3 (66.7%
Eradication or Presumed Eradication = 1/3 (33.3%)
Eradication and Eradication or Presumed Eradication **total** = 3/3 (100%)

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *mefA* genotype] = 2

Patients cured = 2/2 (100%) Eradication = 1/2 (50%)
Eradication or Presumed Eradication = 1/2 (50%)
Eradication and Eradication or Presumed Eradication = 2/2 (100%)

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB / mefA* genotypes] = None.

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *ermB*, *mefA*, or *ermB / mefA* genotypes] = 5

Patients Cured = 5/5 (100%) Eradication = 3/5 (60%)
Eradication or Presumed Eradication = 2/5 (40%)
Eradication and Eradication or Presumed Eradication = 5/5 (100%)

TABLE 51[*] CAP - Japanese Study – Protocol #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) from single pathogen infections by telithromycin MIC susceptibility – PP_b population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome
Number of patients isolated with *Streptococcus pneumoniae* resistant to penicillin (PRSP) = 1	
Patients Cured = 1/1 (100%)	Eradication or Presumed Eradication = 1/1 (100%)

[*] Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

TABLE 52[*] CAP - Japanese Study – Protocol #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) from mixed pathogen infections by telithromycin MIC susceptibility – PP_b population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome
Number of patients isolated with *Streptococcus pneumoniae* resistant to penicillin (PRSP) = 4	
Patients Cured = 4/4 (100%)	Eradication = 2/4 (50%) Eradication or Presumed Eradication = 2/4 (50%)

[*] Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

TABLE 53* CAP - Japanese Study – Protocol #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A, with either *ermB*, *mefA*, or *ermB / mefA* genotypes, from single pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *ermB* or *ermB / mefA* genotypes] = None.

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *me*(A genotype] = 1

Patients Cured = 1/1 (100%) Eradication or Presumed Eradicated = 1/1 (100%)

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G and erythromycin A [with either *ermB*, *mefA*, or *ermB / mefA* genotypes] = 1

Patients Cured = 1/1 (100%) Eradication or Eradication or Presumed = 1/1 (100%)

TABLE 54* CAP - Japanese Study – Protocol #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with either *ermB*, *mefA*, or *ermB / mefA* genotypes] from mixed pathogen infections by telithromycin MIC susceptibility – **PP_b** population at post-therapy/TOC.

Clinical Outcome	Bacteriological Outcome

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *ermB* genotype] = 2

Patients Cured = 2/2 (100%) Eradication = 1/2 (50%)
Eradication or Presumed Eradication = 1/2 (50%)
Eradication and Eradication or Presumed Eradication = 2/2 (100%)

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *mefA* genotype] = 2

Patients Cured = 2/2 (100%) Eradication = 1/2 (50%)
Eradication or Presumed Eradication = 1/2 (50%)
Eradication and Eradication or Presumed Eradication = 2/2 (100%)

Number of patients isolated with *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A [with *ermB / mefA* genotype] = None.

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

Total number of patients isolated with *Streptococcus pneumoniae* isolates resistant to erythromycin A [with *erm*B, *mef*A, or *erm*B / *mef*A genotypes = 4

Patients Cured = 4/4 (100%) Eradication = 2/4 (50%)
Eradication or Presumed Eradication = 2/4 (50%)
Eradication and Eradication or Presumed Eradication = 4/4 (100%)

TABLE 55* CAP: Japanese Studies #2105 and #3107: Subjects with *Streptococcus pneumoniae* isolates resistant to penicillin G and/or erythromycin A from single pathogen infections by telithromycin[a] MIC susceptibility – **PP**[b] population at post-therapy/TOC. Isolate source = sputum.

Study No.	No. Isolates	Teli[b] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #2105 (Patients treated with 600 mg or 800 mg telithromycin)					
ery-R (n = 5)	1[b]	0.03	*erm*B	1 = Cure	1 = Presumed Eradication
	1[b]	0.50	*erm*B	1 = Failure	1 = Eradication
	1	0.016	*erm*B	1 = Cure	1 = Eradication
	1	0.12	*erm*B	1 = Cure	1 = Eradication
	1	0.25	*erm*B	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 3)	1[b]	0.03	*erm*B	1 = Cure	1 = Presumed Eradication
	1	0.06	*erm*B	1 = Cure	1 = Eradication
	1	0.06	*mef*A	1 = Cure	1 = Presumed Eradication
Study #3107 (Patients treated with 600 mg telithromycin)					
ery-R (n = 7)	1	0.03	*erm*B	1 = Cure	1 = Persistence or Recurrence (after temporary Eradication)
	1	0.06	*erm*B	1 = Cure	1 = Eradication or Presumed Eradication
	1	0.06	*erm*B	1 = Cure	1 = Persistence
	1	0.12	*erm*B	1 = Failure	1 = Eradication or Presumed Eradication
	1	0.12	*mef*A	1 = Cure	1 = Eradication or Presumed Eradication
	1	0.12	*erm*B / *mef*A	1 = Cure	1 = Eradication or Presumed Eradication
PRSP / ery-R (n = 1)	1	0.12	*mef*A	1 = Cure	1 = Eradication or Presumed Eradication

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.
[a] Treated with 600 mg (Study #2105); All other patients treated with 800 mg (Study #2105).
[b] teli = telithromycin
n = total number of isolates.

ermB = resistant to macrolides based on methylation of 23S rRNA; *mef*A = resistant to macrolides based on drug efflux; and *mef*A / *ermB* = resistant to macrolides based on both genotypes Study #2105).

Clinical Microbiologist's Comments
The overall bacteriological outcomes (and clinical outcomes) are acceptable. However, the number of resistant *Streptococcus pneumoniae* isolates [PRSP, Ery-A (ermB, mefA), and PRSP / Ery-A] collected from the single pathogen infections are few in number. There are 8-resistant *Streptococcus pneumoniae* collected from Study #2105 and 7-resistant *Streptococcus pneumoniae* collected from Study #3107. In addition, if the *ermB* genotype is present, the MICs are generally very high. Unfortunately, the applicant was not able to obtain strains close to the proposed susceptible breakpoint.

TABLE 56* CAP Japanese Studies #2105 and #3107: Subjects with *Streptococcus pneumoniae* sputum isolates resistant to penicillin G and/or erythromycin A from mixed pathogen infections by telithromycin[a] MIC susceptibility – **PP_b** population at post-therapy/TOC.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #2105 (Patients treated with 800 mg telithromycin)					
ery-R (n = 1)	1	0.06	*ermB*	1= Cure	1 = Presumed Eradication
Study #3107 (Patients treated with 600 mg telithromycin)					
ery-R (n = 1)	1	0.25	*ermB*	1 = Cure	1 = Eradication or Presumed Eradication
PRSP / ery-R (n = 4)	1	0.03	*ermB*	1 = Cure	1 = Eradication
	1	0.12	*ermB*	1= Cure	1 = Eradication or Presumed Eradication
	1	0.12	*mefA*	1 = Cure	1 = Eradication or Presumed Eradication
	1	0.12	*mefA*	1 = Cure	1 = Eradication

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02.

[a] Teli = telithromycin

n = total number of isolates.

ermB = resistant to macrolides based on methylation of 23S rRNA; *mef*A = resistant to macrolides based on drug efflux; and *mef*A / *ermB* = resistant to macrolides based on both genotypes.

PRSP (n = 4)	2	2	—	2 = Cure	2 = Eradication
	2	2	—	2 = Cure	2 = Eradication or Presumed Eradication

Clinical Microbiologist's Comments

The overall bacteriological outcomes (and clinical outcomes) are acceptable. However, the number of resistant *Streptococcus pneumoniae* isolates [PRSP, Ery-A (ermB, mefA), and PRSP / Ery-A] collected from the mixed pathogen infections are very few in number. There is 1 resistant

Streptococcus pneumoniae collected from Study #2105 and 5 resistant *Streptococcus pneumoniae* collected from Study #3107. Also, if the *erm*B genotype is present, the MICs are generally higher.

Acute Exacerbation of Chronic Bronchitis (AECB)

The Applicant conducted a new, Study #3013, in subjects with AECB to provide further efficacy data for *Haemophilus influenzae* and *Moraxella catarrhalis* (irrespective of β-lactamase production by either organism).

Study #3013 is a multicenter, double-blind, randomized, active-controlled, comparative, and 2-arm parallel group. It is an efficacy and safety study of 5 days of oral telithromycin (HMR 3647 800 mg once daily) versus 10 days oral clarithromycin (500 mg twice daily) in the treatment of AECB. The patients are 18 years and older. The primary objective is to demonstrate equivalence in clinical outcomes at the TOC visit. Bacteriological success (eradication or presumed eradication) is a secondary assessment.

The following described clinical and bacteriological data in this Clinical Microbiology Review are from North America, South America, Europe, Africa, and Australia.

AECB Clinical Outcome and Bacteriological Outcome Results at TOC

TABLE 57 **Protocol: #3013 – Per Protocol (PP_b) Population**

Continent	Clinical Outcome	Bacteriological Outcome
North America		
1. Number of patients isolated with *Staphylococcus aureus* at baseline = 1	Patient Failures = 1/1 (100%)	Recurrence = 1/1 (100%)
2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 4	Patients Cured = 2/4 (50%)	Presumed Eradicated = 2/4 (50%)
	Patient Failures = 2/4 (50%)	Persistence = 1/4 (25%)
		Recurrence = 1/4 (25%)
3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 23		
	Patients Cured = 18/23 (78.3%)	Presumed Eradicated = 18/23 (78.3%)
	Patient Failures = 5/23 (21.7%)	Persistence = 3/23 (13.0%)
		Failures = 2/23 (8.7%)
4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 12		
	Patients Cured = 10/12 (83.3%)	Eradication = 1/12 (8.3%)
	Patient Failures = 2/12 (16.7%)	Presumed Eradicated = 8/12 (66.7%)
	Eradicated +	Presumed Eradicated = 9/12 (75%)
		Failures = 2/12 (16.7%)
		Recurrence = 1/12 (8.3%)
South America		
1. Number of patients isolated with *Staphylococcus aureus* at baseline = None		
2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 3		
	Patients Cured = 2/3 (66.7%)	Eradication = 1/3 (33.3%)
	Patient Failures = 1/3 (33.3%)	Presumed Eradicated = 1/3 (33.3%)
	Eradicated +	Presumed Eradicated = 2/3 (66.7%)
		Presumed Persistence = 1/3 (33.3%)
3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 4		
	Patients Cured = 3/4 (75%)	Eradication = 1/4 (25%)
	Patients Failures = 1/4 (25%)	Presumed Eradicated = 2/4 (50%)
		Recurrence = 1/4 (25%)
4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 1		
	Patients Cured = 1/1 (100%)	Presumed Eradicated = 1/1 (100%)

TABLE 57* (con't): Protocol: #3013 – Per Protocol (PP_b) Population

Continent	Clinical Outcome	Bacteriological Outcome

Europe

1. Number of patients isolated with *Staphylococcus aureus* at baseline = 2
   Patients Cured = 2/2 (100%) Eradication = 1/2 (50%)
   Presumed Eradicated = 1/2 (50%)
   Eradicated + Presumed Eradicated = 2/2 (100%)

2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 4
   Patients Cured = 4/4 (100%) Eradication = 1/4 (75%)
   Presumed Eradicated = 3/4 (75%)
   Eradicated + Presumed Eradicated = 4/4 (100%)

3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 4
   Patients Cured = 3/4 (75%) Presumed Eradicated = 3/4 (75%)
   Patient Failures = 1/4 (25%) Presumed Persistence = 1/4 (25%)

4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2
   Patients Cured = 2/2 (100%) Eradication = 1/2 (50%)
   Presumed Eradicated = 1/2 (50%)
   Eradicated + Presumed Eradicated = 2/2 (100%)

Africa

1. Number of patients isolated with *Staphylococcus aureus* at baseline = None

2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 2
   Patients Cured = 2/2 (100%) Presumed Eradicated = 2/2 (100%)

3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2
   Patients Cured = 2/2 (100%) Presumed Eradicated = 2/2 (100%)

4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2
   Patients Cured = 2/2 (100%) Presumed Eradicated = 2/2 (100%)

Australia

1. Number of patients isolated with *Staphylococcus aureus* at baseline = 1
   Patient Failures = 1/1 (100%) Presumed Persistence = 1/1 (100%)

2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = None

3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2
   Patients Cured = 1/2 (50%) Presumed Eradicated = 1/2 (50%)
   Patient Failures = 1/2 (50%) Presumed Persistence = 1/2 (50%)

4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2
   Patients Cured = 2/2 (100%) Eradication = 2/2 (100%)

* Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-5, pp. 481 to 488.

AECB Summary by Specific Pathogen

AECB Clinical Outcome and Bacteriological Outcome Results at TOC

TABLE 58: Protocol: #3013 – Per Protocol (PP_b) Population

Staphylococcus aureus

Continent	Clinical Outcome	Bacteriological Outcome

North America: Number of patients isolated with *Staphylococcus aureus* at baseline = 1
Patient Failures = 1/1 (100%) Recurrence = 1/1 (100%)

South America: Number of patients isolated with *Staphylococcus aureus* at baseline = None

Europe: Number of patients isolated with *Staphylococcus aureus* at baseline = 2
Patients Cured = 2/2 (100%) Eradication = 1/2 (50%)
Presumed Eradicated = 1/2 (50%)
Eradicated + Presumed Eradicated = 2/2 (100%)

Africa: None.

Australia: Number of patients isolated with *Staphylococcus aureus* at baseline = 1
Patient Failures = 1/1 (100%) Presumed Persistence = 1/1 (100%)

* Adapted from this clinical Microbiologist's Review #3 found in Table 57.

Combined Total Number of Patients isolated with *Staphylococcus aureus* at Baseline = 4

Clinical Outcome	Bacteriological Outcome
Patients Cured = 2/4 (50%)	Eradication = 1/4 (25%)
Patient Failures = 2/4 (50%)	Presumed Eradicated = 1/4 (25%)
	Eradicated + Presumed Eradicated = 2/4 (50%)
	Presumed Persistence = 1/4 (25%)
	Recurrence = 1/4 (25%)

The numbers of patients evaluated are very low. The clinical cures are 2/4 (50%) and the bacteriological successes are 2/4 (50%). The clinical failures are 2/4 (50%) and the bacteriological failures are 2/4 (50%), respectively.

TABLE 59: Protocol: #3013 – Per Protocol (PP_b) Population

Streptococcus pneumoniae

Continent	Clinical Outcome	Bacteriological Outcome
North America: Number of patients isolated with *Streptococcus pneumoniae* at baseline = 4		
	Patients Cured = 2/4 (50%)	Presumed Eradicated = 2/4 (50%)
	Patient Failures = 2/4 (50%)	Persistence = 1/4 (25%)
		Recurrence = 1/4 (25%)
South America: Number of patients isolated with *Streptococcus pneumoniae* at baseline = 3		
	Patients Cured = 2/3 (66.7%)	Eradication = 1/3 (33.3%)
	Patient Failures = 1/3 (33.3%)	Presumed Eradicated = 1/3 (33.3%)
		Eradicated + Presumed Eradicated = 2/3 (66.7%)
		Presumed Persistence = 1/3 (33.3%)
Europe: Number of patients isolated with *Streptococcus pneumoniae* at baseline = 4		
	Patients Cured = 4/4 (100%)	Eradication = 1/4 (25%)
		Presumed Eradicated = 3/4 (75%)
		Eradicated + Presumed Eradicated = 4/4 (100%)
Africa: Number of patients isolated with *Streptococcus pneumoniae* at baseline = 2		
	Patients Cured = 2/2 (100%)	Presumed Eradicated = 2/2 (100%)
Australia: Number of patients isolated with *Streptococcus pneumoniae* at baseline = None		

* Adapted from this Clinical Microbiologist's Review #3 found in Table 57.

Combined Total Number of Patients isolated with *Streptococcus pneumoniae* at Baseline = 13

Clinical Outcome	Bacteriological Outcome
Patients Cured = 10/13 (76.9%)	Eradication = 2/13 (15.4%)
Patient Failure = 3/13 (23.1%)	Presumed Eradicated = 8/13 (61.5%)
	Eradicated + Presumed Eradicated = 10/13 (76.9%)
	Persistence = 1/13 (7.7%)
	Presumed Persistence = 1/13 (7.7%)
	Recurrence = 1/13 (7.7%)

The clinical cures and the bacteriological successes are both 10/13 (76.9%). The clinical and the bacteriological failures are also both 3/13 (23.1%), respectively.

TABLE 60: Protocol: 3013 – Per Protocol (PP_b) Population

Haemophilus influenzae

Continent	Clinical Outcome	Bacteriological Outcome
North America: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 23		
	Patients Cured = 18/23 (78.3%)	Presumed Eradicated = 18/23 (78.3%)
	Patient Failures = 5/23 (21.7%)	Persistence = 3/23 (13.0%)
		Failures = 2/23 (8.7%)
South America: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 4		
	Patients Cured = 3/4 (75%)	Eradicated = 1/4 (25%)
	Patient Failures = 1/4 (25%)	Presumed Eradicated = 2/4 (50%)
		Eradicated + Presumed Eradicated = 3/4 (75%)
		Recurrence = 1/4 (25%)
Europe: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 4		
	Patients Cured = 3/4 (75%)	Presumed Eradicated = 3/4 (75%)
	Patient Failures = 1/4 (25%)	Presumed Persistence = 1/4 (25%)
Africa: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2		
	Patients Cured = 2/2 (100%)	Presumed Eradicated = 2/2 (100%)
Australia: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2		
	Patients Cured = 1/2 (50%)	Presumed Eradicated = 1/2 (50%)
	Patient Failures = 1/2 (50%)	Presumed Persistence = 1/2 (50%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 57.

Combined Total Number of Patients isolated with *Haemophilus influenzae* at Baseline = 35

Clinical Outcome	Bacteriological Outcome
Patients Cured = 27/35 (77.1%)	Eradication = 1/35 (2.9%)
Patient Failures = 8/35 (22.9%)	Presumed Eradicated = 26/35 (74.3%)
	Eradicated + Presumed Eradicated = 27/35 (77.1%)
	Persistence = 3/35 (8.6%)
	Presumed Persistence = 2/35 (5.7%)
	Recurrence = 1/35 (2.9%)
	Failures = 2/35 (5.7%)

The clinical cures and the bacteriological successes are both 27/35 (77.1%). The clinical and bacteriological failures are also both 8/35 (22.8%), respectively.

TABLE 61: Protocol: #3013 – Per Protocol (PP_b) Population

Moraxella catarrhalis

Continent	Clinical Outcome	Bacteriological Outcome
North America: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 12		
	Patients Cured = 10/12 (83.3%)	Eradication = 1/12 (8.3%)
	Patient Failures = 2/12 (16.7%)	Presumed Eradicated = 8/12 (66.7%)
		Eradicated + Presumed Eradicated = 9/12 (75%)
		Failures = 2/12 (16.7%)
		Recurrence = 1/12 (8.3%)
South America: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 1		
	Patients Cured = 1/1 (100%)	Presumed Eradicated = 1/1 (100%)
Europe: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2		
	Patients Cured = 2/2 (100%)	Eradication = 1/2 (50%)
		Presumed Eradicated = 1/2 (50%)
		Eradicated + Presumed Eradicated = 2/2 (100%)
Africa: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2		
	Patients Cured = 2/2 (100%)	Presumed Eradicated = 2/2 (100%)
Australia: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2		
	Patients Cured = 2/2 (100%)	Eradication = 2/2 (100%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 57.

Combined Total Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 19

Clinical Outcome	Bacteriological Outcome
Patients Cured = 17/19 (89.5%)	Eradication = 4/19 (21.1%)
Patient Failures = 2/19 (10.5%)	Presumed Eradicated = 12/19 (63.2%)
	Eradicated + Presumed Eradicated = 16/19 (84.2%)
	Recurrence = 1/19 (5.3%)
	Failures = 2/19 (10.5%)

Protocol: #3013 – AECB Per Protocol (PP_b) Summary Analyses

TABLE 62: Combined Clinical Outcome and Bacteriological Outcome Results at TOC

	Staphylococcus aureus	*Streptococcus pneumoniae*	*Haemophilus influenzae*	*Moraxella catarrhalis*
Patients with Isolates	4	13	35	19
Patients Cured	2/4 (50%)	10/13 (76.9%)	27/35 (77.1%)	17/19 (89.5%)
Patient Failures	2/4 (50%)	3/13 (23.1%)	8/35 (22.9%)	2/19 (10.5%)
Microorganisms Eradicated	1/4 (25%)	2/13 (15.4%)	1/35 (2.9%)	4/19 (21.1%)
Microorganisms Presumed Eradicated	1/4 (25%)	8/13 (61.5%)	26/35 (74.3%)	12/19 (63.2%)
Microorganisms (Eradicated + (Presumed Eradicated)	2/4 (50%)	10/13 (76.9%)	27/35 (77.1%)	16/19 (84.2%)
Persistence	None	1/13 (7.7%)	3/35 (8.6%)	None
Presumed Persistence	1/4 (25%)	1/13 (7.7%)	2/35 (5.7%)	None
Recurrence	1/4 (25%)	1/13 (7.7%)	1/35 (2.9%)	1/19 (5.3%)
Failures	None	None	2/35 (5.7%)	2/19 (10.5%)

* Adapted from this Clinical Microbiologist's Review #3 found in Tables 58 to 61.

Microbiologist's Comments:

The Acute Exacerbation of Chronic Bronchitis (AECB) clinical cure outcome rate and bacteriological (i.e., eradication + presumed eradication) outcome rate for the aforemention microorganisms in the Per Protocol (PP_b) population for are as follows:

- For *Staphylococcus aureus*, the Patients Cured and the Bacteriological Outcome (Eradication and Presumed Eradication) are close: 2/4 (50%) and 2/4 (50%), respectively.
- For *Streptococcus pneumoniae* the Patients Cured and the Bacteriological Outcome (Eradication and Presumed Eradication) are close: 10/13 (76.9%) and 10/13 (76.9%), respectively.
- For *Haemophilus influenzae*, the Patients Cured and the Bacteriological Outcome (Eradication and Presumed Eradication) are identical: 27/35 (77.1%) and 27/35 (77.1%), respectively.
- For *Moraxella catarrhalis*, the Patients Cured and the Bacteriological Outcome (Eradication and Presumed Eradication) are close: 17/19 (89.5%) and 16/19 (84.2%), respectively.

Protocol: #3013 – AECB Per Protocol (PP_b) Resistance Data

TABLE 63* AECB: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/mL) or erythromycin resistant (MIC ≥ 1 µg/mL) without centers excluded by FDA - PP_b population. Sample source = sputum.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #3013					
PRSP (n = 1)	1	0.008		1= Cure	1 = Presumed Eradication
ery-R (n = 1)	1	0.030	*erm*B	1= Cure	1 = Presumed Eradication
PRSP / ery-R (n = 1)	1	0.500	*mef*E	1 = Failure	1 = Recurrence

* Adapted from Electronic Document NDA 21-144, EM = 09/12/02, Second Attachment, page 3.

[a] Teli = telithromycin.

n = total number of isolates.

*erm*B = resistant to macrolides based on methylation of 23S rRNA; *mef*A = resistant to macrolides based on drug efflux; and *mef*A / *erm*B = resistant to macrolides based on both genotypes.

Clinical Microbiologist's Comments

There are very few results here. However, for *Streptococcus pneumoniae* which are penicillin-resistant and containing the *erm*B phenotype, the efficacy outcome is acceptable (Cure and Presumed Eradication) with low telithromycin MICs.

AECB Resistant Clinical Outcome and Bacteriological Outcome Results at TOC

TABLE 64* New AECB Protocol: #3013 – Per Protocol (PP_b) Population

Clinical Outcome	Bacteriological Outcome

North America

1. Number of patients isolated with *Staphylococcus aureus* at baseline = 13

Patients Cured = 10/13 (76.9%)	Eradication = 1/13 (7.7%)
Patients Failed = 3/13 (23.1%)	Presumed Eradicated = 10/13 (76.9%)
	Eradication + Presumed Eradicated =11/13 (84.6%)
	Presumed Persistence = 2/13 (15.4%)

2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 20

Patients Cured = 19/20 (95%)	Eradicated = 4/20 (20%)
Patients Failures = 1/20 (5%)	Presumed Eradicated = 15/20 (75%)
	Eradication + Presumed Eradicated = 19/20 (95%)
	Presumed Persistence = 1/20 (5%)

3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 37

Patients Cured = 32/37 (86.5%)	Presumed Eradicated = 31/37 (83.8%)
Patients Failures = 5/37 (13.5%)	Persistence = 1/37 (2.7%)
	Presumed Persistence = 5/37 (13.5%)

4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 6

Patients Cured = 5/6 (83.3%)	Presumed Eradicated = 5/6 (83.3%)
Patient Failures = 1/6 (16.7%)	Presumed Persistence = 1/6 (16.7%)

South America

1. Number of patients isolated with *Staphylococcus aureus* at baseline = None

2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 20

Patients Cured = 18/20 (90%)	Presumed Eradicated = 18/20 (90%)
Patients Failures = 2/20 (10%)	Presumed Persistence = 2/20 (10%)

3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 7

Patients Cured = 6/7 (85.7%)	Presumed Eradicated = 6/7 (85.7%)
Patients Failures = 1/7 (14.3%)	Presumed Persistence =1/7 (14.3%)

4. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 1

Patients Cured = 1/1 (100%)	Recurrence = 1/1 (100%)

Sinusitis

There are no new studies for acute bacterial sinusitis (ABS) in this amendment.

However, 2 studies, #3002 and #3005, were included in the original NDA submission as pivotal trials for 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 *Streptococcus pneumoniae*. This study employed sinus puncture in US patients for microbiological diagnosis.

Clinical outcomes for the aforementioned studies are defined as cure, failure, or indeterminate.

TABLE 65* Sinusitis: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/mL) or erythromycin resistant (MIC ≥ 1 µg/mL) and without centers excluded by FDA - **bmITT** not PP_b population. Sample source = sinus.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #3002					
ery-R (n = 1)	1	0.500	*mef*E	1 = Indeterminate	1 = Indeterminate
Study #3005					
PRSP (n=1)	1	0.016	—	1 = Cure	1 = Presumed Eradication
Study #3011					
ery-R (n =2)	1	0.016	*erm*B	1 = Indeterminate	1 = Indeterminate
	1	0.060	*erm*B	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 2)	1	0.250	*mef*E	1 = Cure	1 = Presumed Eradication
	1	0.016	*erm*B	1 = Cure	1 = Presumed Eradication

* Adapted from NDA 21-144, Electronic Mail Dated 09/12/02.

[a] Teli = telithromycin

n = total number of isolates.

TABLE 66* Sinusitis: Listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/mL) or erythromycin resistant (MIC ≥ 1 µg/mL) and without centers excluded by FDA - **PP_b** population.

Study No.	No. Isolates	Teli[a] MIC (µg/mL)	Genotype	Clinical Outcome	Bacteriological Outcome
Study #3002					
ery-R (n = 5)	1	0.015	*ermB*	1 = Cure	1 = Presumed Eradication
	2	0.060	*ermB*	2 = Cure	2 = Presumed Eradication
	1	1.000	*mefE*	1 = Cure	1 = Presumed Eradication
	1	0.250	*mefE*	1 = Failure	1 = Presumed Persistence
PRSP / ery-R (n = 3)	1	0.030	*ermB*	1 = Cure	1 = Presumed Eradication
	1	0.030[d]	*ermB*	1 = Cure	1 = Presumed Eradication
	1	0.060[d]	*ermB*	1 = Cure	1 = Presumed Eradication
Study #3005					
PRSP / ery-R	1	0.008	*ermB*	1 = Cure	1 = Presumed Eradication
Study #3011					
PRSP (n = 2)	1	0.008	—	1 = Cure	1 = Presumed Eradication
	1	0.008[d]	—	1 = Cure	1 = Presumed Eradication
ery-R (n =5)	3	0.030	*ermB*	1 = Cure	1 = Presumed Eradication
	1	0.060	*ermB*	1 = Cure	1 = Presumed Eradication
	1	0.500	*mefE*	1 = Cure	1 = Presumed Eradication
PRSP / ery-R (n = 7)	1	2.000	*ermB*	1 = Cure	1 = Presumed Eradication
	1	0.060	*mefE*	1 = Cure	1 = Presumed Persistence
	1	0.250	*mefE*	1 = Cure	1 = Presumed Eradication
	2	0.500	*mefE*	1 = Cure	1 = Presumed Eradication
	1	0.012	*mefE*	1 = Failure	1 = Presumed Persistence
	1	0.060	*mefE*	1 = Failure	1 = Presumed Persistence

* Adapted from NDA 21-144, Electronic Mail Dated 09/12/02.

[a] Teli = telithromycin; [b] Penicillin Resistant (MIC = 4 µg/mL)

n = total number of isolates.

There is good telithromycin activity against PRSP, ery-R, and PRSP / ery-R *Streptococcus pneumoniae* isolates. However, clinical "failures" are seen with 1-*mefE* and 2- PRSP / *mefE* *Streptococcus pneumoniae* isolates.

OVERALL SUSCEPTIBILITY DATA & RECOMMENDED BREAKPOINTS

The described susceptibility breakpoint(s) for each pathogen is based on *in vitro* data, animal data, PK/PD data, and *in vivo* (clinical and bacteriological outcomes) data. For additional information refer to Fred Marsik's, Ph.D., Clinical Microbiology Review #1, completed 11/30/00, and Review #2, completed 05/11/02, respectively.

Staphylococcus aureus

1. *In Vitro* Data* of *S. aureus* presented for different populations and susceptibility to telithromycin.

Study	Number Isolates	MIC %-Susceptible	MIC (µg/mL)
Staphylococcus aureus	2,676	100	64
oxacillin-susceptible	2,429	88.3	32
MSSA ery-S	146	90	0.12
MSSA ery-R (IR)	20	90	1
MSSA ery-R (CR)	5	90	> 128
MRSA ery S	20	90	0.25
MRSA ery R (IR)	20	90	0.13
MRSA ery R (CR)	20	90	> 128

* Summary of *In Vitro* Data found in Table 25.

MSSA = methicillin (oxacillin) susceptible *Staphylococcus aureus*
MRSA = methicillin (oxacillin) resistant *Staphylococcus aureus*
IR = inducible-resistant CR = constitutively-resistant

Except for the MSSA Ery-R (CR) and the MRSA Ery R (CR) *Staphylococcus aureus* erythromycin-resistant strains, telithromycin high activity against the other erythromycin-susceptible and –resistant strains. Telithromycin has little activity against the *Staphylococcus aureus* erythromycin constitutively-resistant strains.

The proposed susceptible breakpoint for *S. aureus* is [redacted]. Evaluation of the data presented above suggests that of the MSSA isolated tested, 88% were inhibited by concentrations of ≤32.0 µg/mL. This is somewhat misleading because the data presented in Table 4 of this review shows that 80% of the isolates are inhibited by concentrations of ≤0.25 µg/mL, that 2.3% are inhibited by concentrations of 0.5 to 32.0 µg/mL. In addition, the remaining 10% are inhibited by 64.0 µg/mL. What this data suggests is that we have a bimodal population with most of the MICs falling at the lowest (≤0.25 µg/mL) and highest (64.0 µg/mL) MICs.

2. Microbiological analysis of Clinical Data

a. New CAP Protocols #3012 & #4003 – Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Staphylococcus aureus* at Baseline = 25

Clinical Outcome		Bacteriological Outcome	
Patients Cured	= 21/25 (84%)	Eradication	= 3/25 (12%)

Patients Failures = 4/25 (16%) Presumed Eradicated = 19/25 (76%)
Eradication + Presumed Eradicated = 22/25 (88%)
Presumed Persistence = 3/25 (12%)

The clinical cures are 21/25 (84%) and the bacteriological successes are 22/25 (88%).
The clinical failures are 4/25 (16%) and the bacteriological failures are 3/25 (12%), respectively.

b. New CAP Protocols #3012 & #4003 -- Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Staphylococcus aureus*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

MIC (µg/mL)	=	Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])
0.12	=	8
0.25	=	2
8	=	1

Ninety-one percent of the clinical isolates evaluated had MIC ≤0.25 µg/mL.

c. New AECB Protocol #3013 -- Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Staphylococcus aureus* at Baseline = 4

Clinical Outcome		Bacteriological Outcome	
Patients Cured = 2/4 (50%)		Eradication	= 1/4 (25%)
Patient Failures = 2/4 (50%)		Presumed Eradicated	= 1/4 (25%)
	Eradicated +	Presumed Eradicated	= 2/4 (50%)
		Presumed Persistence	= 1/4 (25%)
		Recurrence	= 1/4 (25%)

The numbers of patients evaluated are very low. The clinical cures are 2/4 (50%) and the bacteriological successes are 2/4 (50%). The clinical failures are 2/4 (50%) and the bacteriological failures are 2/4 (50%), respectively.

d. New AECB Protocols #3013 -- Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Staphylococcus aureus*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

MIC (µg/mL)	=	Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])
0.12	=	2

One hundred percent of the isolates were inhibited by 2.0 µg/mL.

3. Microbiologist's Comments

This Clinical Microbiology Reviewer concurs with Dr. Fred Marsik's recommendation on potential susceptibility breakpoints for *Staphylococcus aureus* as described:

Staphylococcus aureus
(methicillin, erythromycin, and clindamycin susceptible strains only)

MIC (µg/mL)	Interpretation	Disk Diffusion Zone Size (mm)
≤ 0.25	Susceptible (S)	≥ 22

Additional *in vitro* and *in vivo* data were provided in the application. The *in vitro* and in vivo supports the aforementioned recommended susceptibility breakpoint.

Streptococcus pneumoniae

1. *In Vitro* Data* of *S. pneumoniae* presented for different populations and susceptibility to telithromycin.

Study	Number Isolates	MIC (%-Susceptible)	MIC (µg/mL)
Streptococcus pneumoniae	10,103	92.8	0.5
ery-R	3,131	98.8	1
ery-R	5,288	99.2	1
ery-R / *ermB*	657	96.5	0.5
ery-R / *mefA*	436	98.6	0.5
ery-R / *mefA* & *ermB*	71	93	0.5
pen-R	4,027	99.1	1
pen-R	340	97.6	1
levo-R	154	89.6	0.25
pen-R/ery-R/cot-R/tet-R	1,500	99.4	1
pen-R/ery-R/cot-R/tet-R/levo-R	35	100	1
pen-R/ery-R/cot-R/tet-R	129	95.3	0.5

* Summary of *In Vitro* Data found in Table 25.

ery-R = macrolide resistance; *ermB* = macrolide ribosomal methylation resistance mechanism; mefA = macrolide efflux resistance mechanism; pen-R = penicillin resistance; levo-R = levofloxacin resistance; cot-R = co-trimoxazole resistance; and tet-R = tetracycline resistance.

There is a higher MIC (= 1 µg/mL) for PRSP isolates. For macrolide resistant isolates the MIC fluctuates between 0.5 and 1 µg/mL. The proposed susceptible breakpoint for *S. pneumoniae* is 1.0 µg/mL. The in

vitro data presented above and in Table 1 suggests that at least 99% of the population would be considered susceptible. This is irrespective of resistance mechanism. That is, the PRSP and ERSP would also be susceptible. The clinical evidence presented would suggest those patients with *S. pneumoniae* pathogens are clinical and bacteriological successes. However, the PK/PD information required to confirm the breakpoint has not been provided by the applicant. This information will be necessary to confirm the possibility of changing the breakpoint from the current recommendation ([redacted] to the breakpoint proposed by the applicant (1.0 µg/mL).

2. Microbiological analysis of Clinical Data

a. New CAP Protocols #3012 & #4003 -- Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Streptococcus pneumoniae* at Baseline = 144

Clinical Outcome		Bacteriological Outcome	
Patients Cured	= 135/144 (93.8%)	Eradication	= 22/144 (15.2%)
Patients Failures	= 9/144 (6.2%)	Presumed Eradicated	= 117/144 (81.3%)
		Eradication + Presumed Eradicated	= 139/144 (96.5%)
		Presumed Persistence	= 5/144 (3.5%)

The clinical cures are 135/144 (93.8%) and the bacteriological successes are 139/144 (96.5%).

b. New CAP Protocols #3012 & #4003 -- Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Streptococcus pneumoniae*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

Sample Source = all Sputum, except: [b] = Blood and [B.A.L.] = Broncho Alveolar Lavage.

MIC (µg/mL)		Number Clinical and Bacteriological Outcomes (Cures + [Eradication or Presumed Eradication])
0.004	=	2
0.008	=	86 (58 + 25[b] + 3[B.A.L.])
0.016	=	26 (24 + 2[b])
0.030	=	2 (1[b] +1 *erm*A / *erm*B)
0.060	=	4 (2 + 1[b] + 1 *mef*E)
0.120	=	3 (1 + 1[b] + 1 *mef*E)
0.500	=	1 *erm*A / *erm*B
1.000	=	2 (1[b] + 1 *mef*E)

Ninety-one percent of the *S. pneumoniae* have MICs ≤ 0.016 µg/mL.

Macrolide resistance results in higher MICs (≥ 0.030 µg/mL) to telithromycin.

The following table represents clinical and bacteriological failures based on MICs of isolates.

MIC (µg/mL)		Number Isolates		Clinical / Bacteriological Outcome
0.008	=	1[b]	=	Failure / Eradication
0.008	=	2	=	Failure / Presumed Persistence
0.016	=	1	=	Failure / Eradication
0.016	=	1[b]	=	Failure / Eradication
0.016	=	2		Failure / Presumed Persistence
0.120	=	1	=	Failure / Presumed Persistence

[*] Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-2, pp. 429 to 443.

Even at low MICs (≤ 0.12 µg/mL) there are some clinical and bacteriological associated with the use of telithromycin. However, this is not an unusual response since it is also seen with other antimicrobials.

c. New AECB Protocol #3013 -- Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Streptococcus pneumoniae* at Baseline = 13

Clinical Outcome		Bacteriological Outcome	
Patients Cured = 10/13 (76.9%)		Eradication	= 2/13 (15.4%)
Patient Failure = 3/13 (23.1%)		Presumed Eradicated	= 8/13 (61.5%)
	Eradicated +	Presumed Eradicated	= 10/13 (76.9%)
		Persistence	= 1/13 (7.7%)
		Presumed Persistence	= 1/13 (7.7%)
		Recurrence	= 1/13 (7.7%)

The clinical cures and the bacteriological successes are both 10/13 (76.9%). The clinical and the bacteriological failures are also both 3/13 (23.1%), respectively.

d. New AECB Protocols #3013 -- Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Streptococcus pneumoniae*):

The following table represents successful clinical and bacteriological outcomes of sputum isolates based on MICs.

MIC (µg/mL)		Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])
0.008	=	3
0.016	=	5
0.030	=	1

Of the *S. pneumoniae* pathogens analyzed, all had MICs ≤ 0.030 µg/mL and were clinical and bacteriological successes.

The following table represents clinical and bacteriological failures based on MICs of isolates.

MIC (µg/mL)		Number Isolates		Clinical / Bacteriological Outcome
0.008	=	1	=	Failure / Presumed Persistence
0.016	=	1	=	Failure / Persistence
0.500	=	1	=	Failure / Recurrence

* Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-5, pp. 481 to 488.

All 3-clinical and bacteriological failures 3/3 (100%) have MIC ≤ 0.5 µg/mL, respectively. Clearly, there is an overlap of clinical/bacteriological success and failures when analyzed by MIC.

3. The Applicant also provided a CAP listing of subjects with *Streptococcus pneumoniae* penicillin resistant (MIC ≥ 2 µg/L) or erythromycin resistant (MIC ≥ 1 µg/mL) without centers excluded by FDA - **PP_b** population. In summary:

- Telithromycin has good activity against 9-PRSP in the MIC range = 0.008 to 0.030 µg/mL. The clinical outcome are all 9-Cures and the bacteriological outcomes are 2-Eradications and 7-Presumed Eradications.

- Telithromycin has good activity against ery-R phenotype *Streptococcus pneumoniae* isolates in the MIC range = 0.016 to 1.0 µg/mL. The clinical outcome are 15-Cures and 1-Failure (*mef*E phenotype) and the bacteriological outcomes are 4-Eradications and 12-Presumed Eradications.

- Telithromycin has fair activity PRSP/ery-R phenotype *Streptococcus pneumoniae* isolates in the MIC range = 0.060 to 1.000 µg/mL. The clinical outcomes are 10-Cures and 3-Failures (2-*erm*B & 1-*mef*E phenotypes) and the bacteriological outcomes are all 13-Presumed Eradications.

- Of particular interest are the isolates having telithromycin MICs ≥1.0 µg/mL. The microbiological evaluation of the bacteriological per protocol (PP_b) data suggests that of isolates with MICs of 1.0 µg/mL, all three clinical cases, including one bacteremia case, were clinical and bacteriological successes. Also presented were three cases with MICs of 0.5 µg/mL and these were also clinical and bacteriological successes.

4. Microbiologist's Comments

At present, this Clinical Microbiology Reviewer concurs with Dr. Fred Marsiks' recommendation on susceptibility breakpoints for penicillin and erythromycin sensitive *Streptococcus pneumoniae* as described:

Streptococcus pneumoniae
(penicillin and erythromycin susceptible strains only)

MIC (µg/mL)	Interpretation	Disk Diffusion Zone Size (mm)

Additional *in vitro* and *in vivo* data were provided in the application. The *in vitro* and in vivo data supports the aforementioned recommended susceptibility breakpoint. However, the applicant has not determined the disc diffusion and MIC correlation for the proposed breakpoint because the agency has not negotiated the product label. That is, this information has not been relayed to the applicant.

Haemophilus influenzae

1. *In Vitro* Data* of *H. influenzae* presented for different populations and susceptibility to telithromycin.

Study	Number Isolates	MIC %-Susceptible	MIC (µg/mL)
Haemophilus influenzae	2,706	96.2	4
	8,064	92.2	2
β-lact +	1,631	88.2	2

*Summary of *In Vitro* Data found in Table 25.

The MICs fluctuates between 2 and 4 µg/mL whether the isolates are β-lactamase producers or β-lactamase non-producers.

2. Microbiological analysis of Clinical Data

a. New CAP Protocols #3012 & #4003 – Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Haemophilus influenzae* at Baseline = 124

Clinical Outcome		Bacteriological Outcome	
Patients Cured	= 111/124 (89.5%)	Eradication	= 6/124 (4.8%)
Patients Failures	= 13/124 (10.5%)	Presumed Eradicated	= 104/124 (83.9%)
		Eradication + Presumed Eradicated	= 110/124 (88.7%)
		Persistence	= 1/124 (0.8%)
		Presumed Persistence	= 9/124 (7.2%)
		Recurrence	= 4/124 (3.2%)

The clinical cures are 111/124 (89.5%) and the bacteriological successes are 110/124 (88.7%). The clinical failures are 13/124 (10.5%) and the bacteriological failures are 14/124 (11.2%), respectively.

b. New CAP Protocols #3012 & #4003 -- Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Haemophilus influenza*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

MIC (µg/mL)	=	Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])
0.25	=	2
0.5	=	3
1.0	=	22
2.0	=	48
4.0	=	8
8.0	=	6

The data presented in the previous table demonstrate that a majority of the clinical and bacteriological successes occurred in pathogens having MICs of 2.0 to 4.0 µg/mL. The data clearly demonstrates that success is also seen at the proposed breakpoint of 4.0 µg/mL and at the intermediate breakpoint of 8.0 µg/mL. This data would support the proposed breakpoints.

The following table represents clinical and bacteriological failures based on MICs of isolates.

MIC (µg/mL)		Number Isolates	Clinical / Bacteriological Outcome
2.000	=	1	Failure / Eradication
1.000	=	1	Failure / Presumed Eradication
0.500	=	1	Failure / Presumed Persistence
1.000	=	2	Failure / Presumed Persistence
2.000	=	3	Failure / Presumed Persistence
4.000	=	2	Failure / Presumed Persistence
N/A	=	1	Failure / Presumed Persistence
2.000	=	1	Failure / Recurrence
1.000	=	1	Failure / Recurrence

* Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-2, pp. 429 to 443.

All thirteen patients are clinical failures and 12 of these 13 are bacteriological failures at MIC ≥ 0.5 µg/mL, except one bacteriological success at a MIC = 2 µg/mL. These data also suggest that even when the breakpoints suggest success, there will be some failures due to other

risk factors.

c. New AECB Protocol #3013 -- Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Haemophilus influenzae* at Baseline = 35

Clinical Outcome		Bacteriological Outcome	
Patients Cured = 27/35 (77.1%)		Eradication	= 1/35 (2.9%)
Patient Failures = 8/35 (22.9%)		Presumed Eradicated	= 26/35 (74.3%)
	Eradicated +	Presumed Eradicated	= 27/35 (77.1%)
		Persistence	= 3/35 (8.6%)
		Presumed Persistence	= 2/35 (5.7%)
		Recurrence	= 1/35 (2.9%)
		Failures	= 2/35 (5.7%)

The clinical cures and the bacteriological successes are both 27/35 (77.1%). The clinical and bacteriological failures are also both 8/35 (22.8%), respectively.

d. New AECB Protocols #3013 -- Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Haemophilus influenzae*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

MIC (µg/mL)	=	Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])
0.50	=	1
1	=	3
2	=	14
4	=	5
8	=	1

The data presented in the previous table demonstrate that a majority of the clinical and bacteriological successes occurred in pathogens having MICs of 2.0 µg/mL. The data clearly demonstrates that success is also seen at the proposed breakpoint of 4.0 µg/mL and at the intermediate breakpoint of 8.0 µg/mL. As before, this data would support the proposed breakpoints.

The following table represents clinical and bacteriological failures based on MICs of isolates.

MIC (µg/mL)		Number Isolates	Clinical / Bacteriological Outcome
1.000	=	1	Failure / Persistence
2.000	=	1	Failure / Persistence
4.000	=	1	Failure / Persistence
1.000	=	1	Failure / Presumed Persistence
2.000	=	2	Failure / Presumed Persistence
8.000	=	1	Failure / Presumed Persistence
8.000	=	1	Failure / Recurrence

* Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-5, pp. 481 to 488.

All eight patients are clinical and bacteriological failures at MIC ≥ 1.0 µg/mL. These data also suggest that even when the breakpoints suggest success, there will be some failures due to other risk factors.

3. Microbiologist's Comments

This Clinical Microbiology Reviewer concurs with Dr. Fred Marsiks' recommendation on susceptibility breakpoints for *Haemophilus influenzae* as described:

Haemophilus influenzae
(β-lactamase-negative strains only)

MIC (µg/mL)	Interpretation	Disk Diffusion Zone Size (mm)
≤ 4.0	Susceptible (S)	—

Additional *in vitro* and *in vivo* data were provided in the application. The *in vitro* and in vivo supports the aforementioned recommended susceptibility breakpoint. However, the applicant has not determined the disc diffusion and MIC correlation for the proposed breakpoint because the agency has not negotiated the product label. That is, this information has not been relayed to the applicant.

Moraxella catarrhalis

1. *In Vitro* Data*

Moraxella catarrhalis	Number Isolates	MIC %-Susceptible	MIC (µg/mL)
	1,071	99.8	0.06

*Summary of *In Vitro* Data found in Table 25.

MIC_{90} = 0.06 µg/mL.

2. Microbiological analysis of Clinical Data

a. New CAP Protocols #3012 & #4003 – Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 20

Clinical Outcome	Bacteriological Outcome
Patients Cured = 18/20 (90%)	Eradication = 2/20 (10%)
Patients Failures = 2/20 (10%)	Presumed Eradicated = 15/20 (75%)

Eradication +	Presumed Eradicated	= 17/20 (85%)
	Presumed Persistence	= 2/20 (10%)
	Recurrence	= 1/20 (5%)

The clinical cures are 18/20 (90%) and the bacteriological successes are 17/20 (85%).
The clinical failures are 2/20 (10%) and the bacteriological failures are 3/20 (15%), respectively.

b. New CAP Protocols #3012 & #4003 – Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Moraxella catarrhalis*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

MIC (µg/mL)	=	Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])
0.008	=	1
0.06	=	4
0.12	=	3
N/A	=	9

MIC_{100} = 0.12 µg/mL
$MIC_{62.5}$ = 0.06 µg/mL

One hundred percent and sixty-three percent of the *M. catarrhalis* have MICs ≤ 0.12 µg/mL and ≤ 0.06 µg/mL, respectively.

c. New AECB Protocol #3013 – Per Protocol (PP_b) Summary Population Outcome Analyses:

Combined Total Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 19

Clinical Outcome		Bacteriological Outcome		
Patients Cured	= 17/19 (89.5%)	Eradication	= 4/19	(21.1%)
Patient Failures	= 2/19 (10.5%)	Presumed Eradicated	= 12/19	(63.2%)
	Eradicated +	Presumed Eradicated	= 16/19	(84.2%)
		Recurrence	= 1/19	(5.3%)
		Failures	= 2/19	(10.5%)

The clinical cures are 17/19 (89.5%) and the bacteriological successes are 16/19 (84.2%).
The clinical failures are 2/19 (10.5%) and the bacteriological failures are 3/19 (15.8%), respectively.

d. New AECB Protocols #3013 – Per Protocol (PP_b) Summary Population Outcome Analyses by MICs (*Moraxella catarrhalis*):

The following table represents successful clinical and bacteriological outcomes based on MICs of isolates.

MIC (µg/mL)	=	Number Clinical and Bacteriological Outcomes (Cures + [Eradication and/or Presumed Eradication])

0.06	=	2
0.12	=	9
0.25	=	1

$MIC_{91.7}$ = 0.12 µg/mL

---

[a] Summary of *In Vitro* Data, on Page 39.
[b] New CAP Protocols #3012 & #4003 -- Per Protocol (PP_b) Summary Population Analyses, on Page 63
[c] New AECB Protocol # 3013, TABLE 64, Per Protocol (PP_b) Population, on Page 93.

Standardized susceptibility test methods do not exist for the establishment of interpretative criteria *Moraxella catarrhalis*. Thus we can not establish breakpoints.

The following *in vitro* and *in vivo* data are for informational purposes only. Some of the pathogens may be recommend for List #2 (*"in vitro"* only) because there is not enough clinical data to support their inclusion in List #1 (*"in vivo"* only). Susceptibility breakpoints may not be recommended for some pathogens.

Haemophilus parainfluenzae

Microbiological analysis of Clinical Data

a. CAP Clinical Outcomes and Bacteriological Outcomes[c]

Combined Total Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = 40

Clinical Outcome		Bacteriological Outcome		
Patients Cured = 35/40 (87.5%)		Eradication	=	1/40 (2.5%)
Patients Failures = 5/40 (12.5%)		Presumed Eradicated	=	31/40 (77.5%)
	Eradication +	Presumed Eradicated	=	32/40 (80.0%)
		Persistence	=	6/40 (15.0%)
		Presumed Persistence	=	2/40 (5.0%)

The clinical cures are 35/40 (87.5%) and the bacteriological successes are 32/40 (80%).
The clinical failures are 5/40 (12.5%) and the bacteriological failures are 8/40 (20%), respectively.

Mycoplasma pneumoniae

1. *In Vitro* Data[a]

Study	Number Isolates	MIC %-Susceptible	MIC (µg/mL)
Mycoplasma pneumoniae	25	90	0.015

*Summary of *In Vitro* Data found in Table 25.

2. Microbiologist's Comments

Standardized susceptibility test methods do not exist for the establishment of interpretative criteria *Mycoplasma pneumoniae*. Thus we can not establish breakpoints.

Chlamydia pneumoniae

1. *In Vitro* Data*

Study	Number Isolates	MIC %-Susceptible	MIC (µg/mL)
Chlamydia pneumoniae	19	90	0.25

*Summary of *In Vitro* Data found in Table 25.

2. Microbiologist's Comments

Standardized susceptibility test methods do not exist for the establishment of interpretative criteria *Chlamydia pneumoniae*. Thus we can not establish breakpoints.

Legionella pneumophila

1. *In Vitro* Data*

Legionella pneumophila	Number Isolates	MIC %-Susceptible	MIC (µg/mL)
	26	100	0.015

*Summary of *In Vitro* Data found in Table 25.

2. Microbiologist's Comments

Standardized susceptibility test methods do not exist for the establishment of interpretative criteria *Chlamydia pneumoniae*. Thus we can not establish breakpoints.

Clinical Laboratory Susceptibility Test Methods

Microbiology was performed at central laboratories in the United States (CMI, Portland, OR) and in Europe (GR Micro, London). All methods were according to NCCLS recommendations.

Each study site isolated the organisms and screened for antimicrobial susceptibility with a disk diffusion assay. Isolates were then sent to the central labs for re-identification, zone size of inhibition and MIC determinations.

Since 2 central laboratories were involved in producing the microbiological data for the clinical efficacy of telithromycin, there was a validation study conducted by exchange of isolates by the 2 central laboratories.

Previous data that supported establishment of breakpoints for antimicrobial susceptibility testing of targeted pathogens are provided with information from additional clinical trials with telithromycin (e.g., clinical outcome and bacteriologic eradication rates by pathogen by MIC). Material is presented following the guidelines of NCCLS Document M23-A.

Telithromycin was evaluated in 10 clinical laboratories using 2 commercial batches of 15-µg disks ( ). MIC ranges were determined following testing performed per NCCLS guidelines and included 5 different batches of broth.

Proposed Susceptibility Criteria (Breakpoints)

The Applicant's proposed susceptibility and "quality control" breakpoints are as follows:

TABLE 67* Applicant's Proposed Telithromycin Susceptibility Breakpoints

Microorganism	Interpretation MIC (µg/mL)	Interpretation Zone Diameter (mm)
Staphylococcus aureus		
Streptococci, including	≤ 1.0 (S)	≥ 19 (S)

Streptococcus pneumoniae	2.0 (I) ≥ 4.0 (R)	16 – 18 (I) ≤ 15 (R)
Haemophilus influenzae		

* Adopted from NDA 21-144, EDR Dated 07/24/02, on Page 71.
S = susceptible; I = intermediate; R = resistant

The described quality control data is based upon the 10-laboratory study as directed in the NCCLS document, M-23, plus the 30- laboratory "in-life" study and the results from 64 clinical laboratories (clinical trials) the following quality control ranges are proposed.

TABLE 68* Applicant's Proposed Telithromycin Susceptibility Breakpoints - Quality Control Strains

Control Strains	ATCC No.	Interpretation MIC (µg/mL)	Interpretation Zone Diameter (mm)
Enterococcus faecalis			
Haemophilus influenzae	ATCC 49247	1.0 – 4.0	17 - 23
Staphylococcus aureus	ATCC 29213	0.06 – 0.25	NA
Staphylococcus aureus	ATCC 25923	NA	24 - 30
Streptococcus pneumoniae	ATCC 49619		27 - 33

* Adopted from NDA 21-144, EDR Dated 07/24/02, on Page 52.

ATCC = America Type Culture Collection

FDA's Tentative "DRAFT" Telithromycin Susceptibility and "Quality Control" Breakpoints

TABLE 69* FDA's Tentative Telithromycin Susceptibility Breakpoints:**

Microorganism	Interpretation MIC (µg/mL)	Interpretation Zone Diameter (mm)
Staphylococcus aureus (methicillin, erythromycin, and clindamycin susceptible strains only)	≤ 0.25 (S)	≥ 22
Streptococcus pneumoniae		

Haemophilus influenzae
(β-lactamase-negative strains only)

* Adopted from NDA 21-144, EDR Dated 07/24/02, on Page 71.
** Adopted from NDA 21-144, Fred Marsik's Clinical Microbiology Review #2, Date Completed: 05/11/01
** Current absence of data on resistant strains precludes defining any resistant categories other than "susceptible" for telithromycin.

S = susceptible; I = intermediate; R = resistant

TABLE 70* FDA's Proposed Telithromycin Susceptibility Breakpoints - Quality Control Strains:**

Control Strains	ATCC No.	Interpretation MIC (µg/mL)	Interpretation Zone Diameter (mm)
Haemophilus influenzae	ATCC 49247	1 – 4	17 - 23
Streptococcus pneumoniae	ATCC 49619	0.004 – 0.03	27 - 33

* Adopted from NDA 21-144, EDR Dated 07/24/02, on Page 52.
** Adopted from NDA 21-144, Fred Marsik's Clinical Microbiology Review #2, Date Completed: 05/11/01

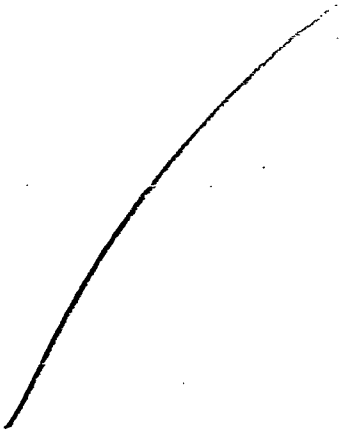
ATCC = America Type Culture Collection

V. CONCLUSIONS FOR NDA 22-144 -- KETEK (telithromycin)

VI. Proposed Labeling for NDA 21-144

(From NDA 21-144, Dr. Fred Marsik's Clinical Microbiology Review #2, Date Completed: 05/11/01)

PROPOSED MICROBIOLOGY PORTION OF PACKAGE LABELING



3 Draft Labeling Page(s) Withheld

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2. National Committee for Clinical Laboratory Standards. *Twelfth Informational Supplement.* NCCLS Document M100- S12 (ISBN 1-56238-454-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2002.

3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 1, No. # (ISBN 1- 56238-393-0). NCCLS, 940 West Valley Road, Wayne, PA 19087-1898, January, 2000.

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

cc: Orig. NDA 20-144
HFD-520/TLMO/J.Alexander
HFD-520/MO/J.Pohlman
HFD-520/MO/C.Cooper
HFD-520/MO/A.Davidson
HFD-520/MO/T.Smith
HFD-725/BM/T.Valappil
HFD-880/BP/J.Zheng
HFD-520/PM/J.Milstein
HFD-520/Micro/H.V.Silver: 01/21; 01/24/03
Filename: N21144HVS-DR#3.doc
APPROVABLE

Concurrence Only:
HFD-520/TLMicro/A.T.Sheldon
RD#1 Initialed 2/4/03 RD#2 1/23/03, Final/24/03 ATS
HFD-520/DepDir/L.Gavrilovich

VII. BIBLIOGRAPHY

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[2] Brown, S., D. Felmingham, and I. Harding. 2002. PROTEKT US 2000/2001. An executive summary of results of the 2000/2001 collection. Document No. UK/02/647/728. GR Micro Ltd., London, Micro research Ltd., Cambs UK. Table 12, Page 36.

[3] Brown, S., D. Felmingham, and I. Harding. 2002. PROTEKT US 2000/2001. An executive summary of results of the 2000/2001 collection. Document No. UK/02/647/728. GR Micro Ltd., London, Micro Research Ltd., Cambs UK. Table 4, Page 28.

[4] Appelbaum, P.C. January 2001. Telithromycin *in vitro* activity against *Streptococcus pneumoniae* isolates resistant to fluoroquinolones. Document No. USA/00/647/676. Hershey Medical Center, Hershey, USA. Pages 14-15.

[5] Bebear C.M., Renaudin H, Bryskier A., and C. Bebear. 2000. Comparative Activities of Telithromycin (HMR 3647), Levofloxacin, and Other Antimicrobial Agents against Human Mycoplasmas. *Antimicrobial Agents & Chemotherapy*. **44**:1981.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Harold Silver
1/24/03 03:35:51 PM
MICROBIOLOGIST

Sign off on the Clinical Microbiology Review #3 on KETEK (telithromycin).

Albert Sheldon
1/27/03 09:34:21 AM
MICROBIOLOGIST

Lillian Gavrilovich
1/31/03 03:41:12 PM
MEDICAL OFFICER

NDA#: 21-144 Addendum (data received after completion of initial review 11/30/00)
Aventis Pharmaceuticals Inc.

Division of Anti-Infective Drug Products
Clinical Microbiology Review # 2

NDA#: 21-144
Date Completed: 5/11/01

Applicant:

Aventis Pharmaceuticals Inc.
10236 Manon Park Drive
PO Box 9627
Kansas City, MO 64134-0627

Contact Person:

J. Michael Nicholas, Ph.D.
Vice President, U.S. Regulatory Affairs, Marketed Products
816-966-5000

Therapeutic Type: Antibacterial

Providing for:

Treatment of: (Applicant revised 3 Apr 2001)

Community Acquired Pneumonia due to:
Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)
Haemophilus influenzae
Moraxella catarrhalis
Chlamydia pneumoniae
Legionella pneumophilia and/or
Mycoplasma pneumoniae

Acute Bacterial Exacerbations of Chronic Bronchitis due to:
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus

Acute Sinusitis due to:
Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)

NDA#: 21-144 Addendum (data received after completion of initial review 11/30/00)
Aventis Pharmaceuticals Inc.

Haemophilus influenzae
Moraxella catarrhalis and/or
Staphylococcus aureus

Tonsillitis/pharyngitis due to:
Streptococcus pyogenes (in patients 13 years old and above)

Product Name:
Proprietary: KETEK™
Established Name: Telithromycin
Code Name/Number: HMR 3647 (RU66647)
Chemical Name: 11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-hexopyranosyl) oxy] 6-O-methyl-3-oxy-12, 11-[oxycarbonyl[[4-[4-(3-pyrindyl)-1H-imidazol-1-yl]butyl]imino]]erythromycin
Chemical formula (empirical): $C_{43}H_{65}N_5O_{10}$
Molecular weight: 812.03

Dosage form: Tablet
Strength: 400 mg
Route of administration: Oral
Dosage/Duration: Two 400 mg tablets daily (800 mg) for 7-10 days for Community Acquired Pneumonia (CAP) and 5 days for Acute Bacterial Exacerbation's of Chronic Bronchitis (ABECB), Acute Sinusitis, and Tonsillitis/Pharyngitis

Dispensed: R_x

Addendum Submission Date(s):
Applicant submission date: 12/19/00
Received by CDER: 12/20/00
Received by reviewer: 12/22/00
Major amendment date: 2/26/01
Received by CDER: 2/17/01
Received by Reviewer: 3/8/01
Review completed:

Supplements/Amendments: Additional data submitted 12/20/00 and 2/15/01 to initial NDA. These data are from study 3010 a community-acquired pneumonia study, and study 3011 an acute maxillary sinusitis study in adults. Study 2105 a Japanese community acquired pneumonia study is a supportive study,

Related Documents: NDA 21-144 dated 3/1/00
Remarks: This is a review only of the data submitted as an addendum of the initial data submitted to the Agency 3/1/00. The Microbiology review of the initial data was completed 11/3//00

TABLE OF CONTENTS

NDA#: 21-144 Addendum (data received after completion of initial review 11/30/00)
Aventis Pharmaceuticals Inc.

MICROBIOLOGY EXECUTIVE SUMMARY

Applicant's Proposed Indications (Applicant revised 3 April 2001):

Treatment of:

Community Acquired Pneumonia due to
Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)
Haemophilus influenzae
Moraxella catarrhalis
Chlamydia pneumoniae
Legionella pneumophilia and/or
Mycoplasma pneumoniae

Acute Bacterial Exacerbations of Chronic Bronchitis due to:
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus (methicillin and erythromycin susceptible strains only)

Acute Sinusitis due to:
Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)
Haemophilus influenzae
Moraxella catarrhalis and/or
Staphylococcus aureus

Tonsillitis/pharyngitis due to:
Streptococcus pyogenes in patients 13 years old and above

Route of administration: Oral
Dosage/Duration: Two 400 mg tablets daily (800 mg) for 7-10 days for Community Acquired Pneumonia (CAP) and 5 days for Acute Bacterial Exacerbation's of Chronic Bronchitis (ABECB), Acute Sinusitis, and Tonsillitis/Pharyngitis

MICROBIOLOGY EXECUTIVE SUMMARY (Cont.)

Pharmacokinetics/Pharmacodynamics

Pharmacokinetics of telithromycin after one dose of 800 mg and 7 days of 800 mg doses in 18 healthy adults

Parameter	Single dose	Seven days
C_{max} (µg/mL)	1.9	2.27
Tmax*	1	1
AUC $_{(0-24)}$ (µg.h/mL)	8.25	12.5
Terminal $t_{1/2}$ (h)	7.16	9.81
C_{24h} (µg/mL)	0.03	0.07

*Median values

In a patient population of 219 subjects, mean peak and trough plasma concentrations were 2.9 and 0.2 µg/mL after 3 to 5 days of 800-mg doses daily.

Telithromycin is 60 to 70% protein bound.

Telithromycin has been shown to concentrate in macrophages and neutrophils above serum levels.

The murine thigh-infection model was used to determine the pharmacokinetic/pharmacodynamic (PK/PD) parameter that is most meaningful in understanding the in vivo efficacy of telithromycin. It was concluded that the 24-hour AUC/MIC ratio is the major determinant of in-vivo activity for HMR 3647. From this data it was concluded that once-daily dosing would be appropriate for HMR 3647.

In Vitro Spectrum of Activity:

Telithromycin has been shown to have in vitro activity against certain Gram-positive bacteria, certain fastidious Gram negative bacteria, some anaerobes, and the atypical pathogens (*Legionella pneumophilia*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*).

Mechanism of Action:

The mode of action of telithromycin (HMR 3647) is inhibition of protein synthesis. This inhibition of protein synthesis occurs by interaction with the bacterial 50S subunit of the ribosome. This inhibits the process of messenger RNA (mRNA) translation. The applicant states that telithromycin also inhibits the assembly of

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

the nascent 50S ribosomal subunit and also the formation of the 30S ribosomal subunit.

Strain variation within groups of organisms determines whether telithromycin is bactericidal or bacteriostatic. The following is generally true. Telithromycin is bactericidal against penicillin and/or erythromycin susceptible and resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. It is bacteriostatic against *S. pyogenes* and *S. aureus*.

Mechanisms of Resistance:

Streptococcus pneumoniae

Streptococcus pneumoniae is resistant to penicillin by modification of the penicillin binding proteins. Telithromycin has activity against penicillin-resistant *S. pneumoniae*.

Macrolide resistance in *S. pneumoniae* can be mediated by the *mef*E gene, a gene encoding an efflux pump mechanism and/or by *erm*B gene, a gene encoding rRNA methylase. Telithromycin has in vitro activity against some strains of *S. pneumoniae* that carry the *mef*E and *erm*B genes. In general when the *mef*E gene is present the telithromycin MIC is elevated while when the *erm*B gene is present the telithromycin MIC is not elevated. Some strains of *S. pneumoniae* have been identified which carry both genes simultaneously.

Genotyping of erythromycin-resistant *S. pneumoniae* (ERSP) isolates from clinical studies done by the Applicant identified 20 strains of ERSP which contained the *mef*E gene and 22 strains that carried the *erm*B gene. Those that carried the *mef*E gene had higher telithromycin MICs than the *S. pneumoniae* that carried the *erm*B gene. The data suggests that there may be concurrent resistance between erythromycin and telithromycin in those strains that carry the *mef*E gene.

Streptococcus pyogenes

Streptococcus pyogenes that carry the *erm* B gene, which encodes for a constitutively produced rRNA methylase, have both a telithromycin MIC_{50} and MIC_{90}, >32µg/mL making them resistant to telithromycin. Telithromycin has in vitro activity against *S. pyogenes* that carry the *erm*A gene (also known as the *erm*TR gene), which encodes for an inducible rRNA methylase.

Genotyping of erythromycin-resistant *S. pyogenes* isolates from clinical studies done by the Applicant showed that of 17 erythromycin-resistant *S. pyogenes* five

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

of the isolates carried the *erm*B gene, nine carried the *mef*A gene and three carried both the *erm*B and *mef*A genes. Four of the five *S. pyogenes* carrying the *erm*B gene had telithromycin MICs of 8 µg/mL making them resistant to therapeutically achievable levels of telithromycin. The other isolates carrying either the *erm*B, *mef*A or both the *erm*B and *mef*A genes had telithromycin MICs ranging from 0.5 to 1 µg/mL. This would have made these isolates of *S. pyogenes* resistant to telithromycin using the Agency's proposed MIC interpretive criteria of _ ⟶ _ for susceptible to telithromycin. Erythromycin-resistant *S. pyogenes* should not be considered to be susceptible to telithromycin.

Staphylococcus aureus

Telithromycin has no activity against methicillin-resistant *S. aureus* or methicillin-resistant coagulase-negative staphylococci. Telithromycin is inactive against *S. aureus* isolates resistant to erythromycin A by a constitutive MLS_B mechanism coded by one the *erm*A, *erm*B, *erm*C or combination of two or three of these genes (MIC>128 µg/mL). Comparable results have been found with coagulase-negative staphylococci having *erm*A, *erm*B or *erm*C genes alone or in combination. Telithromycin has activity against MLS_B inducible strains.

The MIC_{90s} or MIC range of pathogens of interest are given below.

Streptococcus pneumoniae (including penicillin and erythromycin resistant strains):

MIC_{90} = 0.25 µg/mL

Streptococococcus pyogenes:

Erythromycin susceptible MIC_{90} = 0.06 µg/mL

Erythromycin resistant* MIC_{90} = 8 µg/mL

* Resistance due to *erm*B gene.

Staphylococcus aureus

Methicillin susceptible MIC_{90} = 0.3 µg/mL

Methicillin resistant MIC_{90} = >16 µg/mL

Erythromycin and clindamycin resistant = >64 µg/mL