For *S. aureus* a MIC breakpoint of $\leq$ 0.25 µg/mL and a disc diffusion zone size of $\geq$ 22 mm as susceptible with no intermediate or resistant criteria established is appropriate. The determination of criteria defining only telithromycin susceptible *S. aureus* isolates is based on the fact that there is virtually no bacterial eradication or clinical outcome data with *S. aureus* that have MICs higher then 0.25 µg/mL.

INTRACELLULAR BACTERIA

The applicant provided clinical and diagnostic evidence in their previous submissions (NDA 21-144 submitted 28 Feb 00 and NDA 21-144 submitted 26 Feb 01) for the occurrence of 34 cases of *Chlamydia (Chlamydophilia) pneumoniae*, 31 cases of *Mycoplasma pneumoniae* and 13 cases of *Legionella pneumophilia* CAP. In vitro studies have shown that telithromycin concentrates in macrophages and PMNs to concentrations that exceed the MICs of these intracellular pathogens (see "In Vivo" section above). The clinical cure rates for the CAP infections caused by these organisms were demonstrated in clinical trials to be better than 94%. Based on the in vitro susceptibility of these organisms to telithromycin, the fact that telithromycin concentrates in macrophages and the clinical cure rates for these infections demonstrated during clinical trials it would be appropriate to include *C. pneumoniae* and *M. pneumoniae* in the CAP indication. It is not recommended to include *L. pneumophilia* in the CAP indication because of the small number of clinical cases and some discrepancies in the diagnostic test results used to confirm the presence of this organism. It is recommended that *L. pneumophilia* be placed in the "second list" because telithromycin in vitro susceptibility information on better than 100 isolates of the organism shows that the MIC_{90} (see "Spectrum of Activity" above) for the organism is well below the therapeutically achievable concentration of telithromycin that can be achieved in the plasma using the proposed telithromycin dosing regimen, telithromycin concentrates in macrophages, and the organism is relevant to the CAP indication.

SECOND LIST OF BACTERIA

The following bacteria are proposed for the second list based on the fact that they are relevant to the indications, they have MIC_{90s} that indicate they would be susceptible to achievable concentrations of telithromycin based on the dosing regimen and the applicant provided in vitro susceptibility data on $\geq$100 clinical isolates.

Aerobic gram-positive microorganisms

S. pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Viridans group streptococci

Anaerobic bacteria

Prevotella bivia.

Prevotella intermedia

Peptostreptococcus spp.

Other microorganisms

Legionella pneumophila

REFERENCES

1. Wooton M, KE Bowker, A Janowska, et al. 1999. In-vitro activity of HMR 3647 against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis,* and β-haemolytic streptococci. J Antimicrob Chemother *44*:445-453.
2. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Sixth Edition; Approved Standard, NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Eighth Edition; Approved Standard, NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.
4. NCCLS. Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters: Approved Guideline -2nd ed. NCCLS document M23-A2. NCCLS, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898.

WORDING FOR MICROBIOLOGY SECTION OF KETEK PACKAGE INSERT

Microbiology

Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the macrolide family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens. *In vitro*, telithromycin has been shown to demonstrate concentration-dependent bactericidal activity against isolates of *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP*]).

*MDRSP = Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP) penicillin-resistant *Streptococcus pneumoniae*), and isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole

Mechanism of action

Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (e.g., *Streptococcus pneumoniae*) in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin. Telithromycin may also inhibit the assembly of nascent ribosomal units.

Mechanism of resistance

Staphylococcus aureus and *Streptococcus pyogenes* with the constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) phenotype are resistant to telithromycin.

Mutants of *Streptococcus pneumoniae* derived in the laboratory by serial passage in subinhibitory concentrations of telithromycin have demonstrated resistance based on L22 riboprotein mutations (telithromycin MICs are elevated but still within the susceptible range), one of two reported mutations affecting the L4 riboprotein, and production of K-peptide. The clinical significance of these laboratory mutants is not known.

Cross resistance

Telithromycin does not induce resistance through methylase gene expression in erythromycin-inducibly resistant bacteria, a function of its 3-keto moiety. Telithromycin has not been shown to induce resistance to itself.

List of Microorganisms

Telithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical settings as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin and erythromycin susceptible isolates only)

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP*])

*MDRSP=Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*), and are isolates resistant to two or more of the following antimicrobials:

penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Haemophilus influenzae

Moraxella catarrhalis

Other microorganisms

Chlamydophila (Chlamydia) pneumoniae

Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for telithromycin. However, the safety and efficacy of telithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Viridans group streptococci

Anaerobic bacteria

Prevotella bivia

Prevotella intermedia

Peptostreptococcus spp.

Other microorganisms

Legionella pneumophila

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution

methods (broth or agar dilution)[1,3] or equivalent with standardized inoculum and concentrations of telithromycin powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibiotics. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg telithromycin to test the susceptibility of microorganisms to telithromycin. Disc diffusion zone sizes should be interpreted according to criteria in Table

Table Susceptibility Test Result Interpretive Criteria for Telithromycin

	Minimal Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R[a]	S	I	R[a]
Staphylococcus aureus	≤ 0.25			≥ 22		
Streptococcus pneumoniae	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
Haemophilus influenzae	≤ 4	8	≥ 16	≥ 15	12-14	≤ 11

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antibacterial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control:

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures[1,2,3]. Standard telithromycin powder should provide the MIC ranges for the quality control organisms in Table For the disk diffusion technique, the 15-µg telithromycin disk should provide the zone diameter ranges for the quality control organisms in Table

Table Acceptable Quality Control Ranges for Telithromycin

QC Strain	Minimum Inhibitory Concentration (µg/mL)	Disk Diffusion (Zone diameter in mm)
Staphylococcus aureus ATCC® 29213	0.06 - 0.25	Not Applicable
Staphylococcus aureus ATCC 25923	Not Applicable	24 - 30
Streptococcus pneumoniae ATCC 49619	0.004 - 0.03	27- 33
Haemophilus influenzae ATCC 49247	1.0 - 4.0	17- 23

ATCC = American Type Culture Collection

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Sixth Edition; Approved Standard, NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Eighth Edition; Approved Standard, NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing: Fourteenth Informational Supplement; Approved Standard, NCCLS Document M2-A8 and M7-A6, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2004.

_____ Date:_____
Frederic J. Marsik, Ph.D.
Microbiology Reviewer

CONCURRENCE ONLY

RD#2 and Final Initialed 03/29/04 ATS
HFD-520/TLMicro/AT Sheldon, Jr., Ph.D.

_____ Date:_____
HFD-520/DepDir/L Gavrilovich, M.D.

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/s/

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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

Clinical Microbiological Review

NDA#: 21-144 **REVIEW #: 3** **COMPLETED DATE: 12/31/02**

Reviewer: Harold V. Silver

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
21-144	07/24/02	07/24/02	07/30/02

NAME & ADDRESS OF APPLICANT:

Aventis Pharmaceuticals Inc.
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U.S. Regulatory Liaison,
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SUBMISSION REVIEWED:

An amendment for the treatment of the following proposed indications due to the following organisms:

Community Acquired Pneumonia (CAP):

- For subjects [redacted]
- Treatment / Duration: Two 400 mg tablets daily (800 mg) for 7 to 10 days
- Due to :

Staphylococcus aureus
Streptococcus pneumoniae (including strains resistant to penicillin G and/or the macrolides)
Haemophilus influenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

Acute Bacterial Exacerbation of Chronic Bronchitis (AECB):

- For subjects 18 years and above
- Treatment / Duration: Two 400 mg tablets daily (800 mg) for 5 days
- Due to:

Staphylococcus aureus
Streptococcus pneumoniae (including strains resistant to penicillin G and/or the macrolides)
Haemophilus influenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)

Acute Sinusitis (AS) due to:

- For subjects [redacted]
- Treatment / Duration: Two 400 mg tablets daily (800 mg) for 5 days

- Due to:

Staphylococcus aureus
Streptococcus pneumoniae (including strains resistant to penicillin G and/or the macrolides)
Haemophilus influenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)

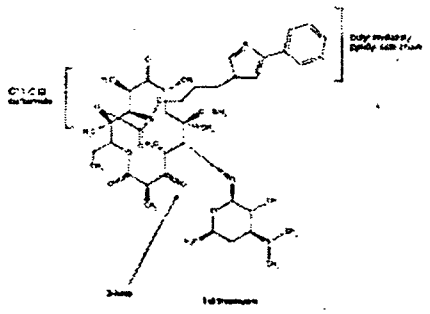
Note: See Fred Marsik, Ph.D., Clinical Microbiology Review #1 (11/30/00) and Review #2 (05/11/01) for more information on the Acute Sinusitis (AS) indication.

Tonsillitis / Pharyngitis due to *Streptococcus pyogenes* (patients 13 years old and above) is not requested in this Amendment dated 07/24/02. Therefore, the indication and proposed targeted microorganisms are not addressed in Clinical Microbiology Review #3.

DRUG PRODUCT NAME:

Proprietary:	KETEK™ Tablets
Non-Proprietary/USAN:	telithromycin
Code Names:	HMR3647, HMR3647A (Adult oral) RU 66647
Empirical Formula:	$C_{43}H_{65}N_5O_{10}$
Molecular weight:	812.03

Structure*:



* Adopted from NDA 21-144, EDR Dated 07/24/02, on Page 49.

DOSAGE FORM: Tablet
POTENCY: 400 mg telithromycin / tablet
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

RELATED DOCUMENT(s): IND 55,283

PHARMACOLOGICAL CATEGORY: Semisynthetic antibacterial (ketolide); related to the macrolides.

FDA APPROVED INDICATIONS: None yet.
REMARKS/COMMENTS:

This is the 3rd Clinical Microbiology Review on NDA 21-144, KETEK (telithromycin). The re-submission (amendment) and an e-mail (EM) dated 09/12/02 which contains new additional clinical microbiology data on the Applicant's proposed indications.

For more information see Fred Marsik, Ph.D., Clinical Microbiology Reviewer, DAIDP/HFD-520, completed Clinical Microbiology Review #1 and Review #2 on 11/30/00 and 05/11/01, respectively.

MICROBIOLOGY EXECUTIVE SUMMARY

Description

Semisynthetic antibacterial

Belongs to the ketolide family of antimicrobials within the macrolide-lincosamide-streptogramin (MLS_B) class.

Mechanism of Action

Inhibition of bacterial protein synthesis by binding to 23S ribosomal RNA.

Spectrum of Activity

In vitro activity against Gram-positive bacteria, fastidious Gram-negative bacteria, some anaerobes, and atypical pathogens (*Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*).

Bacteriostatic against: *Staphylococcus aureus* and *Streptococcus pyogenes*.

Bactericidal against penicillin – or erythromycin-susceptible and -resistant *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

None to minimal activity against methicillin-resistant *Staphylococcus aureus* or methicillin-resistant coagulase-negative staphylococci.

MIC_{90} of pathogens of interest are described as follows:

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

In vitro activity against some strains of *Streptococcus pneumoniae*, that carries the *mef*E and/or *erm*B genes.

Mechanism of Resistance

The MLS_B phenotype confers cross-resistance to macrolides, lincosamides, and streptogramins. The MLS_B phenotype is encoded in pneumococci by genes belonging to the *erm*B or *erm*A class. The mechanism of resistance is by ribosomal methylation.

Another mechanism of resistance is by active efflux of erythromycin due to the *mef*E gene, renamed *mef*A.

Other Microbiologic Characteristics of Telithromycin

Synergism: No data available.

Antagonism: No data available.

Post-Antibiotic Effect (PAE): Telithromycin has been shown to have a PAE ranging from approximately 1 hr. to 8 hrs. at 10x MIC against the pathogens of interest.

pH Effect: A decrease in pH from 7 to 5.5 increases the telithromycin MIC for *Streptococcus pneumoniae* by approximately 15 fold.

Inoculum Effect: Increasing inoculum size from 10^4 to 10^5 cfu/mL does not effect the MIC. If the inoculum size is 10^7 or greater, the telithromycin MIC for *Streptococcus pneumoniae* goes up approximately 2 to 4-fold.

CO_2 Effect: Incubation in 6% CO_2 results in approximately a 2-fold increase in telithromycin MIC values against *Streptococcus pneumoniae* and *Haemophilus influenzae*

SUMMARY DESCRIPTION OF THE CLINICAL STUDIES

Community Acquired Pneumoniae (CAP)

There are 2 new Community Acquired Pneumoniae (CAP) studies, Protocols #3012 and #4003.

Study #3012: This is an open-label, multicenter, multinational, uncontrolled, non-comparative study of the efficacy and safety of 7 days of oral telithromycin (HMR3647 800 mg once daily) in the treatment of community-acquired pneumoniae due to *Streptococcus pneumoniae* in adolescents and adults; and

Study #4003: This is a double-blind, multicenter, multinational, active-controlled study of the efficacy and safety of oral HMR3647 (800 mg once daily) 5 days versus 7 days versus 10 days of oral clarithromycin (500 mg twice daily) in the treatment of community-acquired pneumoniae.

Note: PP_b = All PP_c subjects with isolation of a causative pathogen from an adequate culture of pre-therapy or entry.

PP_c = All mITT subjects except those with major protocol violations and/or indeterminate responses.

Japanese Community Acquired Pneumoniae (CAP) Clinical Studies

The following 2-studies may be considered supportive studies:

- Japanese 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.

- Japanese Study #3107 is an investigation of the efficacy and safety of HMR3647 600 mg (q.d.) and levofloxacin 300 mg (100 mg t.i.d.), double-blind, randomized, drug-controlled, non-inferiority comparative study.

Summary

- The overall bacteriological outcomes from the submitted resistant data [ery-R (*erm*B, *mef*A), and PRSP / ery-R] are collected from the single pathogen infections. There are 8-resistant *Streptococcus pneumoniae* isolates collected from Study #2105 and 7-resistant *Streptococcus pneumoniae* isolates collected from Study #3107. When the *erm*B genotype is present, the MICs are generally higher.

- The overall bacteriological outcomes from the submitted resistant data are acceptable. However, the number of resistant *Streptococcus pneumoniae* isolates [PRSP, ery-R (*erm*B, *mef*A), and PRSP / ery-R] collected from the mixed pathogen infections are very small. There is 1-resistant *Streptococcus pneumoniae* collected from Study #2105 and 5-resistant *Streptococcus pneumoniae* collected from Study #3107. Again, when 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 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 above. The clinical and bacteriological data are collected from North America, South America, Europe, Africa, and Australia.

CLINICAL MICROBIOLOGIST'S SUMMARY ANALYSES OF THE CLINICAL AND BACTERIOLOGICAL RESULTS

The summary analyses show *in vitro* and *in vivo* data that demonstrates the activity and efficacy of telithromycin as described:

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 has high activity against the other erythromycin-susceptible and –resistant strains. Telithromycin has little activity against the *Staphylococcus aureus* erythromycin constitutively-resistant strains.

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 *S. aureus* have MICs ≤ 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 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.

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 / *erm*B	657	96.5	0.5

ery-R / *mef*A	436	98.6	0.5
ery-R / *mef*A & *erm*B	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

ery-R = macrolide resistance; *erm*B = macrolide ribosomal methylation resistance mechanism; *mef*A = 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.

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 and/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 and one half of these isolates have a MIC ≤ 0.016 µg/mL. In general, strains containing

macrolide resistant determinants have higher MICs than strains that do not.
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

Even at low MICs (≤ 0.12 µg/mL) there are some clinical and bacteriological failures 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 based on MICs of isolates.

Sample Source = Sputum.

MIC (µg/mL)		Number Clinical and Bacteriological Outcomes (Cures + [Eradication 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

All 3-clinical and bacteriological failures 3/3 (100%) have MIC ≤ 0.5 µg/mL, respectively.

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

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 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])
0.25	=	2
0.5	=	3
1.0	=	22
2.0	=	48
4.0	=	8
8.0	=	6

Ninety-three percent of the strains have MICs ≤4.0 µg/mL.

The following table represents clinical and/or 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

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

Nine-six percent of the *H. influenzae* have MICs ≤ 4.0 µg/mL

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.

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.

The Applicant also provided a CAP listing of subjects with *Streptococcus pneumoniae* with either 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 *ermB* & 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, [redacted] 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.

Recommended Susceptibility Breakpoints and Ranges for Targeted Microorganisms

The additional new *in vitro* and *in vivo* data concurs and supports the susceptibility breakpoints and ranges as originally recommended by Fred Marsik, Ph.D., Clinical Microbiology Reviewer, DAIDP/HFD-520. The additional new data were combined with the previous data reviewed and evaluated previously by Dr. Fred Marsik. Therefore, the described recommended susceptibility breakpoints and ranges for the targeted microorganisms are as follows:

Microorganism	MIC (µg/mL)	Interpretation	Disk Diffusion Zone Size (mm)
Staphylococcus aureus (methicillin, erythromycin, and clindamycin susceptible strains only)	≤ 0.25	Susceptible	≥ 22
Streptococcus pneumoniae (penicillin and/or erythromycin susceptible strains)	[redacted]		
Haemophilus influenzae (β-lactamase-negative strains only)	[redacted]		

Note: Other organisms and additional data may be considered during the weeks up to and following the Advisory Committee Meeting on January 8-9, 2003.

Standardized susceptibility test methods do not exist for the establishment of interpretative criteria for *Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila*. Thus we can not establish breakpoints.

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I. INTRODUCTION

KETEK (telithromycin), NDA 21-144, was originally submitted on 02/28/00. Aventis Pharmaceuticals Inc., received an "approvable" letter on 06/01/01. The applicant was asked to submit additional data on CAP/ABS clinical studies targeting resistant pathogens, CAP/ABECB/ABS safety and clinical pharmacology, and additional data on ABECB targeted organisms.

The need to overcome resistance, and particularly to provide activity against penicillin G and/or macrolide-(erythromycin A)- resistant strains of *Streptococcus pneumoniae*, has driven the development of new compounds designed to overcome multiply drug-resistant pneumococci. The ketolides represent a new class of drugs resulting from this research.

Ketolides are semisynthetic — The word ketolide is derived from keto (3-keto group) and olide (lactone). The defining chemical characteristic of the ketolides is a 3-keto function on erythromycin A in lieu of the usual cladinose. This imparts the following biological properties to the compound:

- High stability under acidic conditions which enhances the ability of the drug to pass through the stomach. After 6 hours contact with a solution of pH 1.0, greater than 90% of the antibacterial activity of telithromycin remains.

- Inability to induce MLS_B resistance. Ketolides also exhibit antibacterial activity against *erm*-containing gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pneumoniae.*

- Substitution of the C11-C12 hydroxyl groups of the erythromycin A ring with a carbamate residue results in additional beneficial properties which complement those imparted by the 3-keto function.

- The C11-C12 carbamate residue enhances antibacterial activity in comparison to erythromycin A and confers the ability to overcome resistance to erythromycin A and other macrolides resulting from an efflux mechanism.

- Antibacterial activity against the emerging ribosomal L4 and L22 protein mutants.

- The butyl pyridyl side chain attached to the C11-C12 carbamate residue is also responsible for the antibacterial activity, mode of action, intracellular uptake, and efflux of the compound.

- Reduced impact of efflux mechanism of resistance.

- Enhanced antibacterial activity against gram-positive bacteria.

- Governs intracellular accumulation and efflux in phagocytes.

Note: For additional clinical microbiology information on pertinent areas (spectrum of activity, mechanism of resistance, PK/PD) the reader is referred to Fred Marsik, Ph.D., Clinical Microbiology Reviewer, DAIDP/HFD-520, completed Clinical Microbiology Review #1 and Review #2 on 11/30/00 and 05/11/01, respectively.

II. PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

Erythromycin A, clarithromycin, and azithromycin prevent bacterial protein synthesis by binding to specific sites in the bacterial ribosome and interfering with elongation of nascent polypeptide chains. In addition, these compounds interfere with the formation of the 50S ribosomal subunit.

Ribosomes are the functional units of translation. Bacterial ribosomes consist of ribonucleoprotein particles having a sediment coefficient of 70S. The 70S ribosome is composed of 2 subunits: 30S and 50S particles. The 30S subunit is made up of 16S ribosomal ribonucleic acid (rRNA) and 21 different proteins. The 50S subunit consists of 2 rRNA molecules: 23S rRNA and 5S rRNA, and 33 proteins. The main function of the 50S ribosomal subunit is to promote peptide bond formation. Six distinct structural domains have been found in the 23S rRNA, and 5S rRNA forms a structural link between domain II and domain V. Further, 5S rRNA may assist in the proper juxtaposition of domain II and V in the ribosomal tertiary structure.

The macrolides and ketolides have a second target for inhibition of protein synthesis among susceptible bacteria, interference with the assembly of nascent 50S ribosomal subunits following binding to a specific receptor on the 50S precursor particle. Incomplete particles are then subject to degradation by bacterial ribonucleases, leading to gradual depletion of functional ribosomes and accumulation of RNA oligonucleotides within the cells. This inhibition of assembly of the 50S ribosomal subunit is a lethal event for bacterial cells due to ribonuclease digestion of the ribosomal RNAs. When concentrations of the compound are reached that essentially halt protein synthesis, telithromycin also reduces formation of the 30S ribosomal subunits, an additional mechanism for lethal disruption of ribosomal subunit formation.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The Applicant submitted new *in vitro* data on the organisms listed below. These data came from the Applicant's PROTEKT surveys. Susceptibility testing was performed using NCCLS susceptibility procedures and susceptibility interpretative criteria for those antimicrobial drugs that have interpretative criteria.

***Streptococcus pneumoniae*:**

TABLE 1[*] shows comparative MICs of telithromycin and other antibiotics against *Streptococcus pneumoniae* isolates USA (n = 10,103).

Antimicrobial	MIC (mg/L) %													
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Telithromycin	59.85	11.82	2.24	6.69	4.12	8.07	6.84	0.37			0.01			
Penicillin			48.4	12.4	4.78	3.56	4.36	15	10.6	0.8				
Amox/clav				66.1	2.34	3.16	11.7	7.69	4.63	4.4				
Cefuroxime				57.5	6.9	2.44	1.73	2.47	13.9	11.9	3.09			
Clindamycin					91.1	0.27	0.45	8.16						
Erythromycin			49	19.4	0.26	0.19	0.28	0.75	4.41	7.24	18.5			
Clarithromycin		34	34	0.55	0.29	0.34	0.81	4.47	5.68	9.68	10.2			
Azithromycin		1.06	6.26	50.1	10.7	0.44	0.34	0.43	2.26	6.09	22.3			
Levofloxacin				0.06	0.34	12.6	82.9	3.11	0.15	0.27	0.4	0.2		
Gatifloxacin			0.3	3.11	72.6	22.8	0.32	0.17	0.37	0.39				
Tetracycline			1.05	20.9	57	4.46	0.36	0.18	0.25	15.8				
Linezolid			0.06	0.09	0.53	4.84	51.1	43.3	0.09					
Co-trimoxazole					55.5	3.34	4.87	2.36	10.6	23.4				

[*] Adopted from NDA 21-144, EDR Dated 07/24/02, see Review Reference 1.

Telithromycin ($MIC_{92.8} \leq 0.5$ mg/L, n = 9,376 isolates) is more active than the macrolide, erythromycin ($MIC_{100} \leq 16$ mg/L), clarithromycin ($MIC_{89.8} \leq 8$ mg/L), and the azalide, azithromycin ($MIC_{100} \leq 16$ mg/L), agents tested against the 10,103 *Streptococcus pneumoniae* isolates USA. The data clearly demonstrates a population shift in MIC in favor of telithromycin versus the macrolides and the azalide antimicrobials. The proposed susceptible breakpoint for *Streptococcus pneumoniae* is 1.0 mg/L. From this table, we can see that this would encompass greater than 99% of the tested isolates. We will need to evaluate the pharmacokinetics, pharmacodynamics and the clinical and bacteriological outcome data to determine the final breakpoint.

Haemophilus influenzae:

TABLE 2* shows the comparative MICs of telithromycin and other antibiotics against *Haemophilus influenzae* isolates USA (n = 2,706).

Antimicrobial	MIC (mg/L) %													
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Telithromycin					0.57	0.3	1.37	16.1	62.4	15.5	3.12	0.3	0.3		
Ampicillin							62.6	7.42	0.95	1.52	27.5				
Amox-clav							84.9	10.7	3.46	0.72	0.27				
Cefprozil					1.37	0.76	7.46	14.2	20.5	19.8	17	18.9			
Cefuroxime					2.66	6.77	39.3	31.3	9.47	7.04	2.93	0.3	0.19		
Cefotaxime					98.9	0.68	0.38								
Clarithromycin						0.38	0.19	0.38	2.59	10.5	50.2	29.1	5.86	0.91	
Azithromycin					0.53	1.33	3.84	29.6	46.5	16.2	1.45	0.27	0.3		
Levofloxacin				98.9	0.42		0.08		0.08	0.08	0.19	0.27			
Gatifloxacin			98.1	1.03	0.15	0.08	0.08	0.04	0.04	0.3	0.15				
Moxifloxacin			91.6	6.92	0.68	0.23	0.08		0.04	0.11	0.38				
Tetracycline				0.34	1.14	15.9	79.2	2.17	0.27	0.04	0.23	0.68			
Linezolid								0.08	0.42	0.67	10.7	65	21.9	1.03	

* Adopted from NDA 21-144, EDR Dated 07/24/02, see Review Reference 2.

Telithromycin ($MIC_{96.2} \leq 4$ mg/L, 2,603 isolates) and the azalide, azithromycin ($MIC_{98} \leq 4$ mg/L) are more active than the macrolide, clarithromycin ($MIC_{93.3} \leq 16$ mg/L), agent tested against the 2,706 *Haemophilus influenzae* isolates USA. The telithromycin MIC data are normally distributed with a mode of 2.0 mg/L. The proposed susceptible breakpoint for *Haemophilus influenzae* is 4.0 mg/L. From this table, we can see that this would encompass greater than 96% of the tested isolates. We will need to evaluate the pharmacokinetics, pharmacodynamics and the clinical and bacteriological outcome data to determine the final breakpoint.

The PROTEKT Surveys and Susceptibility Studies

The applicant performed PROTEKT surveys. PROTEKT, known as Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin, is an international antimicrobial susceptibility survey of community-acquired bacterial respiratory tract pathogens. PROTEKT US was established in 2000 to study the antimicrobial susceptibility of common bacterial pathogens (e.g., *Streptococcus pneumoniae*) isolated from patients with community-acquired respiratory tract infections spread geographically throughout the USA.

The aim of the survey is to either chart emergence and spread of important resistant phenotypes and genotypes, to determine the activity of telithromycin against those strains, and/or to compare telithromycin activity with the activity of competitive antimicrobials.

PROTEKT US 2000/2001 (UK/02/647/728

The Applicant's PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) US 2000/2001 was established in 2000 to study the antimicrobial

susceptibility of common bacterial pathogens isolated from patients with community-acquired respiratory tract infections spread geographically throughout the USA. The isolates included *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus influenzae*. Following re-identification of the isolates, a central laboratory determined minimum inhibitory concentrations (MICs) using the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution method.

PROTEKT Worldwide 1999/2000 Winter Season (UK/02/647/727)

The Applicant's PROTEKT Worldwide 1999/2000 winter season surveillance study is similar to the aforementioned PROTEKT US 2000/2001 surveillance study. However, the isolates included *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Legionella pneumophila*. PROTEKT included data from Asia, North America, Europe (Eastern Europe & Western European), Latin America, and Australasia (Australia & Indonesia). MICs were determined using the NCCLS broth microdilution method.

PROTEKT Worldwide 2000/2001 (UK/02/647/729)

The Applicant's PROTEKT Worldwide 2000/2001 surveillance study is similar to the aforementioned PROTEKT 1999/2000 surveillance study. However, the isolates included only *Streptococcus pneumoniae* and *Haemophilus influenzae*. PROTEKT included data from Asia, North America, Europe (Eastern Europe & Western European), Latin America, and Australasia (Australia & Indonesia). MICs were determined using the NCCLS broth microdilution method.

The following described data shows results from the Applicant's susceptibility studies and the PROTEKT surveys. Resistance data are presented too.

***Staphylococcus aureus*:**

TABLE 3* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 2,676 isolates of *Staphylococcus aureus* recovered in the PROTEKT surveillance program 2000, US and 2001).

	EMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Oxacillin	Levo-floxacin	Cotri-moxazole
S.aureus									
0.008	4 (0.1 %)	34 (1.3 %)	-	-	-	-	-	-	-
0.015	12 (0.4 %)	229 (8.6 %)	-	-	-	-	-	-	-
0.03	333 (12.4 %)	301 (11.3 %)	1 (0.0 %)	1 (0.0 %)	-	35 (1.3 %)	1301 (48.6 %)	-	-
0.06	2034 (76.0 %)	342 (12.8 %)	2 (0.1 %)	25 (0.9 %)	2 (0.1 %)	587 (18.8 %)	1955 (73.1 %)	-	-
0.12	2131 (79.6 %)	381 (14.2 %)	114 (4.3 %)	928 (34.7 %)	-	2117 (79.1 %)	2028 (75.8 %)	-	2401 (89.7 %)
0.25	2140 (80.0 %)	440 (16.4 %)	1469 (54.9 %)	1701 (63.6 %)	129 (4.8 %)	2146 (80.2 %)	2044 (76.4 %)	-	2491 (93.1 %)
0.5	2148 (80.3 %)	564 (21.1 %)	1720 (64.3 %)	1719 (64.2 %)	962 (35.9 %)	2151 (80.4 %)	2079 (77.7 %)	2014 (75.3 %)	2519 (94.1 %)
1	2154 (80.5 %)	717 (26.8 %)	1724 (64.4 %)	1727 (64.5 %)	1718 (64.2 %)	2153 (80.5 %)	2291 (85.6 %)	2045 (76.4 %)	2538 (94.8 %)
2	2157 (80.6 %)	879 (32.8 %)	1730 (64.6 %)	1734 (64.8 %)	1728 (64.6 %)	-	2429 (90.8 %)	2115 (79.0 %)	2558 (95.6 %)
4	2161 (80.8 %)	1132 (42.3 %)	1741 (65.1 %)	1753 (65.5 %)	1732 (64.7 %)	2165 (80.9 %)	2584 (96.6 %)	2185 (86.1 %)	2567 (95.9 %)
8	2184 (81.6 %)	2676(100.0 %)	1761 (65.8 %)	1749 (65.1 %)	1738 (65.0 %)	2676(100.0 %)	2676(100.0 %)	2438 (91.1 %)	2582 (96.5 %)
16	2187 (81.7 %)	-	1774 (66.3 %)	1781 (66.6 %)	1754 (65.5 %)	-	-	2577 (96.3 %)	2605 (97.3 %)
32	2202 (82.3 %)	-	1783 (66.6 %)	1812 (67.7 %)	1769 (66.1 %)	-	-	2643 (98.8 %)	2676(100.0 %)
64	2676(100.0 %)	-	1818 (67.9 %)	2676(100.0 %)	1805 (67.5 %)	-	-	2676(100.0 %)	-
128	-	-	2676(100.0 %)	-	2676(100.0 %)	-	-	-	-
Total	2676	2676	2676	2676	2676	2676	2676	2676	2676

* Adopted from NDA 21-144, EDR Dated 07/24/02, Page 42 (refer to Table 40 on Page 367).

The ketolide, telithromycin (MIC_{100} ≤ 64 µg/mL, n = 2,676) is the most active against the 2,676 strains of *Staphylococcus aureus* recovered in the PROTEKT surveillance program 2000, US and 2001. Although some isolates had higher MICs to telithromycin than other comparative antimicrobials, much larger numbers of *Staphylococcus aureus* were susceptible to lower concentrations of telithromycin (lower MICs) than to other antimicrobial drugs.

The azalide, azithromycin, MIC_{100} ≤128 µg/mL (n = 2,676), and the macrolides, erythromycin MIC_{100} ≤ 128 µg/mL (n = 2,676), and clarithromycin, MIC_{100} ≤ 64 µg/mL (n = 2,676).

TABLE 4* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 2,429 isolates of *Staphylococcus aureus* (oxacillin-susceptible) recovered in the PROTEKT surveillance program 2,000, US and 2001).

***Staphylococcus aureus* (oxacillin-susceptible):**

S.aureus (OXA-S)																					
0.008	4	(0.2 %)	34	(1.4 %)	-		-		-		-		34	(1.4 %)	1301	(53.6 %)	-		-		
0.015	12	(0.5 %)	227	(9.3 %)	-		-		-		-		-		-		-		-		
0.03	327	(13.5 %)	301	(12.4 %)	1	(0.0 %)	1	(0.0 %)	-		-		34	(1.4 %)	1301	(53.6 %)	-		-		
0.06	1995	(82.1 %)	340	(14.0 %)	2	(0.1 %)	25	(1.0 %)	2	(0.1 %)	492	(20.3 %)	1955	(80.5 %)	-		-		-		
0.12	2089	(86.0 %)	379	(15.6 %)	113	(4.7 %)	923	(38.0 %)	-		2074	(85.4 %)	2029	(83.5 %)	-		2213	(91.1 %)			
0.25	2097	(86.3 %)	437	(18.0 %)	1464	(60.3 %)	1696	(69.8 %)	128	(5.3 %)	2102	(86.5 %)	2044	(84.1 %)	-		2281	(93.9 %)			
0.5	2105	(86.7 %)	558	(23.0 %)	1715	(70.6 %)	1714	(70.6 %)	959	(39.5 %)	2106	(86.7 %)	2079	(85.6 %)	2014	(82.9 %)	2306	(94.9 %)			
1	2111	(86.9 %)	709	(29.2 %)	1719	(70.8 %)	1722	(70.9 %)	1713	(70.5 %)	2108	(86.8 %)	2281	(94.3 %)	2045	(84.2 %)	2316	(95.3 %)			
2	2113	(87.0 %)	868	(35.7 %)	1725	(71.0 %)	1729	(71.2 %)	1723	(70.9 %)	-		2429	(100.0 %)	2115	(87.1 %)	2329	(95.9 %)			
4	2114	(87.0 %)	1115	(45.9 %)	1736	(71.5 %)	1748	(72.0 %)	1727	(71.1 %)	2116	(87.1 %)	-		2303	(94.8 %)	2337	(96.2 %)			
8	2131	(87.7 %)	2429	(100.0 %)	1756	(72.3 %)	1764	(72.6 %)	1734	(71.4 %)	2429	(100.0 %)	-		2418	(99.5 %)	2351	(96.8 %)			
16	2133	(87.8 %)	-		1769	(72.8 %)	1776	(73.1 %)	1749	(72.0 %)	-		-		2429	(100.0 %)	2371	(97.6 %)			
32	2144	(88.3 %)	-		1778	(73.2 %)	1802	(74.2 %)	1764	(72.6 %)	-		-		-		2429	(100.0 %)			
64	2429	(100.0 %)	-		1808	(74.4 %)	2429	(100.0 %)	1799	(74.1 %)	-		-		-		-				
128	-		-		2429	(100.0 %)	-		2428	(100.0 %)	-		-		-		-				
Total	2429		2429		2429		2429		2429		2429		2429		2429		2429				

	HMR 3647	Pani-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Oxacillin	Levo-floxacin	Cotri-moxazole

* Adopted from NDA 21-144, EDR Dated 07/24/02, Page 42 (refer to Table 40 on Page 367).

The ketolide, telithromycin, $MIC_{88.3}$ ≤ 32 µg/mL (n = 2,144) is the most active against the 2,429 strains of *Staphylococcus aureus* recovered in the PROTEKT surveillance program 2000, US and 2001. Note that these MICs are lower for oxacillin sensitive *Staphylococcus aureus* (TABLE 5).

The azalide, azithromycin, MIC_{100} ≤ 128 µg/mL (n = 2,429), and the macrolides, erythromycin MIC_{100} ≤ 128 µg/mL (n = 2,429), and clarithromycin, MIC_{100} ≤ 64 µg/mL (n = 2,429).

TABLE 5* shows the antibacterial spectrum of telithromycin and clarithromycin against *Staphylococcus aureus* isolates with various patterns of inducible (IR) and constitutively (IC) erythromycin A-resistant resistance.

		Telithromycin		Clarithromycin	
S. aureus	**N**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**
MSSA Ery-S	146	0.06	0.12	0.12	0.25
MSSA Ery-R (IR)	20	0.5	1	>128	>128
MSSA Ery-R (CR)	5	>128	>128	>128	>128
MRSA Ery S	20	0.13	0.25	0.5	0.5
MRSA Ery R (IR)	20	0.13	0.13	>128	>128
MRSA Ery R (CR)	20	>128	>128	>128	>128

* Adopted from NDA 21-144, EDR Dated 07/24/02, Table on Page 75 and Previous submitted Microbiology, Table 16 on page 100.

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.

Streptococcus pneumoniae:

TABLE 6* shows the MIC cumulative distribution to selected antibiotics when testing strains of *Streptococcus pneumoniae* for PROTEKT protocol(s) US.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Chlora-mphenicol
S.pneumoniae									
0.015	5047 (59.9 %)	-	-	-	-	-	-	-	-
0.03	7241 (71.7 %)	-	-	3451 (34.2 %)	113 (1.1 %)	-	-	-	-
0.06	7467 (73.9 %)	4939 (48.8 %)	4998 (49.5 %)	6090 (68.2 %)	738 (7.3 %)	-	-	-	-
0.12	8143 (80.6 %)	6160 (61.0 %)	6924 (68.6 %)	6944 (68.7 %)	5836 (57.8 %)	-	5823 (57.6 %)	7 (0.1 %)	-
0.25	8559 (84.7 %)	6638 (65.7 %)	6952 (68.8 %)	6974 (69.0 %)	6981 (69.1 %)	9212 (91.2 %)	6518 (64.5 %)	37 (0.4 %)	5588 (55.3 %)
0.5	9374 (92.8 %)	6986 (69.2 %)	6972 (69.0 %)	7009 (69.4 %)	6943 (68.7 %)	9239 (91.4 %)	6765 (67.0 %)	1338 (13.2 %)	5938 (58.8 %)
1	10065 (99.6 %)	7442 (73.7 %)	7001 (69.3 %)	7031 (70.2 %)	6977 (69.1 %)	9282 (91.9 %)	6941 (68.7 %)	9698 (96.0 %)	6438 (63.7 %)
2	10102 (100.0 %)	8862 (88.7 %)	7077 (70.0 %)	7538 (74.6 %)	7028 (69.5 %)	10103 (100.0 %)	7194 (71.2 %)	10014 (99.1 %)	6679 (66.1 %)
4	-	10021 (99.2 %)	7512 (74.4 %)	8106 (80.2 %)	7247 (71.7 %)	-	8602 (85.1 %)	10022 (99.2 %)	7737 (76.6 %)
8	-	10103 (100.0 %)	8239 (81.6 %)	9078 (89.9 %)	7854 (77.7 %)	-	9795 (97.0 %)	10046 (99.4 %)	10103 (100.0 %)
16	10103 (100.0 %)	-	10103 (100.0 %)	10103 (100.0 %)	10103 (100.0 %)	-	10103 (100.0 %)	10084 (99.8 %)	-
32	-	-	-	-	-	-	-	10103 (100.0 %)	-
Total	10103	10103	10103	10103	10103	10103	10103	10103	10103

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table 8 on Page 185. and Review Reference 3.

Telithromycin ($MIC_{92.8} \leq 0.5$ mg/L, n = 9,374) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 16$ mg/L, n = 10,1031) and clarithromycin ($MIC_{89.9} \leq 8$ mg/L, n = 9,078), and the azalide, azithromycin ($MIC_{100} \leq 16$ mg/L, n = 10,103) agents when tested against the 10,103 *Streptococcus pneumoniae* isolates.

The susceptibility breakpoint for clindamycin (an lincosamide) against *Streptococcus pneumoniae* ≤ 0.25 µg/mL. TABLE 7 shows the clindamycin $MIC_{91.2} \leq 0.25$ mg/L (9,212 / 10,103). Since some of the *Streptococcus pneumoniae* isolates are resistant (≥ 0.5 µg/mL), the MLS_B phenotype may be present.

Macrolide-Resistant (ery-R) Strains

Streptococcus pneumoniae (ery-R):

TABLE 7* shows the MIC cumulative distribution to selected antibiotics when testing strains of erythromycin A-resistant *Streptococcus pneumoniae* for PROTEKT protocol(s) US.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (ERY-R)									
0.015	57 (1.8 %)	-	-	-	-	-	-	-	-
0.03	302 (9.6 %)	-	-	2 (0.1 %)	-	-	-	-	-
0.06	507 (16.2 %)	242 (7.7 %)	-	4 (0.1 %)	3 (0.1 %)	-	-	-	-
0.12	1173 (37.5 %)	416 (13.3 %)	-	-	5 (0.2 %)	-	339 (10.8 %)	2 (0.1 %)	-
0.25	1588 (50.7 %)	582 (18.6 %)	-	9 (0.3 %)	6 (0.2 %)	2166 (72.4 %)	539 (17.2 %)	8 (0.2 %)	370 (11.8 %)
0.5	2462 (78.7 %)	766 (24.5 %)	-	38 (1.2 %)	-	2585 (73.0 %)	686 (21.7 %)	569 (18.2 %)	428 (13.7 %)
1	3093 (98.8 %)	3056 (122.7 %)	29 (0.9 %)	120 (3.8 %)	14 (0.4 %)	2310 (73.8 %)	743 (24.4 %)	3012 (96.2 %)	600 (19.2 %)
2	3130 (100.0 %)	2160 (69.0 %)	185 (5.4 %)	567 (18.1 %)	52 (1.7 %)	3131 (100.0 %)	905 (28.9 %)	3082 (98.8 %)	692 (22.1 %)
4	-	3072 (99.1 %)	540 (17.2 %)	1134 (36.2 %)	276 (8.8 %)	-	1906 (60.9 %)	3097 (98.9 %)	1427 (45.6 %)
8	-	3131 (100.0 %)	1267 (40.5 %)	2166 (67.3 %)	802 (28.2 %)	-	2928 (93.5 %)	3106 (99.2 %)	3131 (100.0 %)
16	3131 (100.0 %)	-	3131 (100.0 %)	3131 (100.0 %)	3131 (100.0 %)	-	3131 (100.0 %)	3124 (99.8 %)	-
32	-	-	-	-	-	-	-	3131 (100.0 %)	-
Total	3131	3131	3131	3131	3131	3131	3131	3131	3131

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table 8 on Page 185.

Telithromycin ($MIC_{98.8} \leq 1$ µg/L, n = 3,039) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 16$ mg/L, n = 3,131) and clarithromycin ($MIC_{100} \leq 16$ mg/L, n = 3,131), and the azalide, azithromycin ($MIC_{100} \leq 16$ mg/L, n = 3,131) when tested against 3,131 erythromycin A-resistant *Streptococcus pneumoniae* isolates. Note that the erythromycin resistant MIC breakpoint is ≥ 1.0 µg/mL and 98.8% of these isolates are susceptible to telithromycin at a MIC ≤1.0 µg/mL. In addition, the penicillin MIC for resistance is ≥ 2.0 µg/mL and the data suggests that about 65% of the isolates evaluated are resistant to penicillin. Of these isolates, 98% have a telithromycin MIC ≤1.0 µg/mL. These data clearly show that telithromycin has better intrinsic activity than erythromycin and penicillin when measured as weight / volume (µg/mL).

TABLE 8* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 5,288 isolates of erythromycin A-resistant *Streptococcus pneumoniae* recovered in the PROTEKT surveillance program.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (ERY-R)									
0.008	32 (0.6 %)	41 (0.8 %)	-	-	-	-	-	-	-
0.015	431 (8.2 %)	257 (4.9 %)	-	-	-	-	2 (0.0 %)	-	-
0.03	1107 (20.9 %)	443 (8.4 %)	-	2 (0.0 %)	-	34 (0.6 %)	196 (3.7 %)	-	-
0.06	1847 (34.9 %)	893 (16.9 %)	-	4 (0.1 %)	3 (0.1 %)	648 (12.3 %)	346 (6.5 %)	-	-
0.12	2836 (53.6 %)	1180 (22.3 %)	-	-	5 (0.1 %)	738 (14.0 %)	788 (14.9 %)	2 (0.0 %)	66 (1.2 %)
0.25	3523 (66.6 %)	1480 (28.0 %)	-	10 (0.2 %)	6 (0.1 %)	3015 (57.0 %)	1125 (21.3 %)	8 (0.2 %)	895 (16.9 %)
0.5	4517 (85.4 %)	1768 (33.5 %)	-	66 (1.2 %)	10 (0.2 %)	3043 (57.5 %)	1421 (26.9 %)	1524 (28.8 %)	1202 (22.7 %)
1	5244 (99.2 %)	2215 (41.9 %)	84 (1.6 %)	262 (5.0 %)	40 (0.8 %)	3075 (58.2 %)	1640 (31.0 %)	5088 (96.2 %)	1737 (32.8 %)
2	5283 (99.9 %)	3927 (74.3 %)	369 (7.0 %)	977 (18.5 %)	179 (3.4 %)	3904 (73.8 %)	1870 (35.4 %)	5189 (98.1 %)	1923 (36.4 %)
4	5285 (99.9 %)	5199 (98.3 %)	1023 (19.5 %)	1668 (31.5 %)	694 (13.1 %)	3959 (74.9 %)	3368 (63.7 %)	5202 (98.4 %)	2952 (55.8 %)
8	5287 (100.0 %)	5288 (100.0 %)	1927 (36.4 %)	2805 (53.0 %)	1498 (28.3 %)	5288 (100.0 %)	4977 (94.1 %)	5227 (98.8 %)	5059 (95.7 %)
16	5288 (100.0 %)	-	3863 (73.1 %)	3875 (73.3 %)	3847 (72.7 %)	-	5288 (100.0 %)	5278 (99.8 %)	5178 (97.9 %)
32	-	-	3879 (73.4 %)	3944 (74.6 %)	3857 (72.9 %)	-	-	5288 (100.0 %)	5288 (100.0 %)
64	-	-	3941 (74.5 %)	5288 (100.0 %)	3918 (74.1 %)	-	-	-	-
128	-	-	5288 (100.0 %)	-	5288 (100.0 %)	-	-	-	-
Total	5288	5288	5288	5288	5288	5288	5288	5288	5288

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 25 and to Table 2 on Page 145.

Telithromycin ($MIC_{99.2} \leq 1$ µg/mL, n = 5,244) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 16$ µg/mL, n = 10,1031) and clarithromycin ($MIC_{100} \leq 128$ µg/mL, n = 5,288), and the

azalide, azithromycin (MIC_{100} ≤ 128 µg/mL, n = 5,288), agents when tested against 5,288 erythromycin A-resistant *Streptococcus pneumoniae* isolates.

MLS_B Mechanism (*erm*B genotype)

The Applicant stated that in the combined PROTEKT database, of the 657 isolates confirmed to be resistant to macrolides based on methylation of 23S rRNA, 99.5% were susceptible to no more than 1.0 µg/mL of telithromycin. Based on molecular analysis of isolates recovered in the PROTEKT US program, 17.3% of all macrolide resistant pneumococci were of the *erm*B genotype.

Organisms resistant by this mechanism are typically cross-resistant to the macrolide, lincosamide, and streptogramin B classes of antibacterial agents (MLS_B). Only 2.3% of these strains were reported to be susceptible to clindamycin.

Streptococcus pneumoniae (ery-R / *erm*B):

TABLE 9[*] shows the comparative in vitro activities of antibacterial agents commonly prescribed for the treatment of RTIs against 657 isolates of erythromycin A-resistant *Streptococcus pneumoniae* harboring *erm*B genome identified in the PROTEKT surveillance program.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae	(ERY-R/ermB)								
0.008	13 (2.0 %)	10 (1.5 %)	-	-	-	-	-	-	-
0.015	140 (21.3 %)	51 (7.8 %)	-	-	-	-	1 (0.2 %)	-	-
0.03	313 (47.6 %)	88 (13.5 %)	-	-	-	-	41 (6.2 %)	-	-
0.06	425 (64.7 %)	146 (22.2 %)	-	-	-	8 (1.2 %)	74 (11.3 %)	-	-
0.12	491 (74.7 %)	190 (28.8 %)	-	-	-	14 (2.1 %)	106 (16.1 %)	-	7 (1.1 %)
0.25	543 (82.6 %)	236 (35.9 %)	-	-	-	15 (2.3 %)	154 (23.4 %)	-	104 (15.8 %)
0.5	634 (96.5 %)	266 (40.5 %)	-	-	-	16 (2.4 %)	198 (30.1 %)	272 (41.4 %)	164 (25.0 %)
1	654 (99.5 %)	323 (49.2 %)	1 (0.2 %)	3 (0.5 %)	-	-	238 (36.2 %)	624 (95.8 %)	258 (39.3 %)
2	655 (99.7 %)	524 (79.8 %)	2 (0.3 %)	-	-	-	269 (40.9 %)	635 (96.7 %)	292 (44.4 %)
4	656 (99.8 %)	645 (98.2 %)	3 (0.5 %)	5 (0.8 %)	1 (0.2 %)	46 (10.0 %)	396 (60.3 %)	639 (97.3 %)	382 (58.1 %)
8	657(100.0 %)	657(100.0 %)	8 (1.2 %)	9 (1.4 %)	5 (0.8 %)	657(100.0 %)	610 (92.8 %)	644 (98.0 %)	559 (85.1 %)
16	-	-	8 (1.4 %)	12 (1.8 %)	7 (1.1 %)	-	657(100.0 %)	656 (99.8 %)	612 (93.2 %)
32	-	-	12 (1.8 %)	46 (10.0 %)	-	-	-	657(100.0 %)	657(100.0 %)
64	-	-	43 (8.6 %)	657(100.0 %)	58 (8.8 %)	-	-	-	-
128	-	-	657(100.0 %)	-	657(100.0 %)	-	-	-	-
Total	657	657	657	657	657	657	657	657	657

[*] Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 26 and to Table 2 on Page 145.

Telithromycin ($MIC_{96.5}$ ≤ 0.5 µg/mL, n = 634) is more active than the macrolide, erythromycin A (MIC_{100} ≤ 128 µg/mL, n = 657) and clarithromycin (MIC_{100} ≤ 64 µg/mL, n = 657), and the azalide, azithromycin (MIC_{100} ≤ 128 µg/mL, n = 657), when tested against 657 erythromycin A-resistant / *erm*B *Streptococcus pneumoniae* isolates.

Macrolide Efflux Resistance

Streptococcus pneumoniae (ery-R / *mef*A):

TABLE 10[*] shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 436 isolates of erythromycin A-resistant *Streptococcus pneumoniae* harboring *mef*A genome identified in the PROTEKT surveillance program.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (ERY-R/mefA)									
0.008	1 (0.2 %)	8 (1.8 %)	-	-	-	-	-	-	-
0.015	2 (0.5 %)	50 (11.5 %)	-	-	-	-	-	-	-
0.03	11 (2.5 %)	92 (21.3 %)	-	-	-	9 (2.1 %)	35 (8.0 %)	-	-
0.06	149 (34.2 %)	109 (25.0 %)	-	-	-	108 (24.8 %)	83 (19.0 %)	-	-
0.12	245 (56.2 %)	125 (28.7 %)	-	-	-	361 (82.8 %)	98 (22.5 %)	-	4 (0.9 %)
0.25	354 (81.2 %)	140 (32.1 %)	-	-	-	-	109 (25.0 %)	-	80 (18.3 %)
0.5	430 (98.6 %)	150 (34.4 %)	-	10 (2.3 %)	-	-	126 (28.9 %)	151 (34.6 %)	116 (26.6 %)
1	436 (100.0 %)	169 (38.8 %)	11 (2.5 %)	44 (10.1 %)	8 (1.8 %)	362 (83.0 %)	128 (29.4 %)	426 (97.2 %)	202 (46.3 %)
2	-	295 (67.7 %)	77 (17.7 %)	170 (39.0 %)	37 (8.5 %)	-	144 (33.0 %)	428 (98.2 %)	221 (50.7 %)
4	-	427 (97.9 %)	223 (51.1 %)	245 (56.2 %)	180 (41.3 %)	369 (84.6 %)	227 (52.1 %)	429 (98.4 %)	266 (61.0 %)
8	-	436 (100.0 %)	308 (70.6 %)	326 (74.8 %)	289 (66.3 %)	436 (100.0 %)	391 (89.7 %)	431 (98.9 %)	351 (80.5 %)
16	-	-	353 (81.0 %)	355 (81.4 %)	349 (80.0 %)	-	436 (100.0 %)	435 (99.8 %)	382 (87.9 %)
32	-	-	361 (82.8 %)	367 (84.2 %)	357 (81.9 %)	-	-	436 (100.0 %)	436 (100.0 %)
64	-	-	369 (84.6 %)	436 (100.0 %)	367 (84.2 %)	-	-	-	-
128	-	-	436 (100.0 %)	-	436 (100.0 %)	-	-	-	-
Total	436	436	436	436	436	436	436	436	436

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 27 and to Table 2 on Page 146.

Telithromycin ($MIC_{98.6} \leq 0.5$ µg/mL, n = 430) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 128$ µg/mL, n = 436) and clarithromycin ($MIC_{100} \leq 64$ µg/mL, n = 436), and the azalide, azithromycin ($MIC_{100} \leq 128$ µg/mL, n = 436) agents when tested against 436 erythromycin A-resistant / *mef*A *Streptococcus pneumoniae* isolates.

Macrolide Resistance

Streptococcus pneumoniae (ery-R / *mef*A & *erm*B):

TABLE 11* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 71 isolates of erythromycin A-resistant *S. pneumoniae* harboring both *mefA* and *ermB* genome identified in the PROTEKT surveillance program.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (ERY-R/mefA & ermB)									
0.06	1 (1.4 %)	2 (2.8 %)	-	-	-	2 (2.8 %)	1 (1.4 %)	-	-
0.12	7 (9.9 %)	-	-	-	-	-	-	-	-
0.25	18 (25.4 %)	4 (5.6 %)	-	-	-	-	3 (4.2 %)	-	1 (1.4 %)
0.5	66 (93.0 %)	5 (7.0 %)	-	-	-	-	4 (5.6 %)	26 (36.6 %)	4 (5.6 %)
1	71 (100.0 %)	8 (11.3 %)	-	-	-	-	-	69 (97.2 %)	9 (12.7 %)
2	-	20 (28.2 %)	-	-	-	-	6 (8.5 %)	70 (98.6 %)	12 (16.9 %)
4	-	44 (80.1 %)	-	1 (1.4 %)	-	7 (9.9 %)	15 (21.1 %)	-	17 (23.9 %)
8	-	71 (100.0 %)	2 (2.8 %)	2 (2.8 %)	2 (2.8 %)	71 (100.0 %)	41 (57.7 %)	71 (100.0 %)	58 (78.4 %)
16	-	-	-	-	-	-	71 (100.0 %)	-	62 (87.3 %)
32	-	-	-	7 (9.9 %)	-	-	-	-	71 (100.0 %)
64	-	-	7 (9.9 %)	71 (100.0 %)	7 (9.9 %)	-	-	-	-
128	-	-	71 (100.0 %)	-	71 (100.0 %)	-	-	-	-
Total	71	71	71	71	71	71	71	71	71

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 28 and to Table 2 on Page 146.

Telithromycin ($MIC_{93} \leq 0.5$ µg/mL, n = 66) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 128$ µg/mL, n = 71) and clarithromycin ($MIC_{100} \leq 64$ µg/mL, n = 71), and the azalide, azithromycin ($MIC_{100} \leq 128$ µg/mL, n = 71) agents when tested against 71 erythromycin A-resistant / *mef*A & *erm*B *Streptococcus pneumoniae* isolates

Penicillin Resistance

Penicillin-Resistant *Streptococcus pneumoniae* (PRSP) Strains

TABLE 12* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 4,027 penicillin G-resistant isolates of *Streptococcus pneumoniae* (PRSP) recovered in the PROTEKT surveillance program.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae [PEN-R]									
0.004	2 (0.0 %)	-	-	-	-	-	-	-	-
0.008	230 (5.7 %)	-	-	-	-	-	-	-	-
0.015	984 (24.7 %)	-	-	4 (0.1 %)	-	-	-	-	-
0.03	1399 (34.7 %)	-	53 (1.3 %)	436 (10.3 %)	4 (0.1 %)	23 (0.6 %)	-	-	-
0.06	1790 (44.4 %)	-	665 (16.5 %)	951 (22.1 %)	98 (2.4 %)	649 (16.1 %)	-	-	-
0.12	2406 (59.7 %)	-	939 (23.3 %)	941 (23.4 %)	725 (18.0 %)	749 (18.6 %)	1 (0.0 %)	-	2 (0.0 %)
0.25	2751 (68.3 %)	-	947 (23.5 %)	947 (23.5 %)	935 (23.2 %)	2815 (69.9 %)	-	1 (0.0 %)	210 (5.2 %)
0.5	3382 (84.0 %)	-	954 (23.7 %)	972 (24.1 %)	943 (23.4 %)	2832 (70.3 %)	2 (0.0 %)	1043 (25.9 %)	350 (8.7 %)
1	3998 (99.3 %)	-	984 (24.4 %)	1067 (26.5 %)	962 (23.9 %)	2843 (70.6 %)	6 (0.1 %)	3901 (96.9 %)	623 (15.5 %)
2	4022 (99.9 %)	2406 (59.7 %)	1139 (28.3 %)	1531 (38.0 %)	1038 (25.8 %)	3419 (84.9 %)	59 (1.5 %)	3955 (98.2 %)	714 (17.7 %)
4	4024 (99.9 %)	3912 (97.1 %)	1572 (39.0 %)	1858 (46.1 %)	1252 (31.1 %)	3435 (85.3 %)	1690 (42.0 %)	3962 (98.4 %)	1618 (40.0 %)
8	4026(100.0 %)	4027(100.0 %)	2121 (52.7 %)	2735 (67.8 %)	1840 (45.7 %)	4027(100.0 %)	3611 (89.7 %)	3979 (98.8 %)	3751 (93.1 %)
16	4027(100.0 %)	-	3405 (84.6 %)	3406 (84.6 %)	3399 (84.4 %)	-	4027(100.0 %)	4013 (99.7 %)	3898 (96.8 %)
32	-	-	3409 (84.7 %)	3424 (85.0 %)	3404 (84.5 %)	-	-	4027(100.0 %)	4027(100.0 %)
64	-	-	3425 (85.1 %)	4027(100.0 %)	3420 (84.9 %)	-	-	-	-
128	-	-	4027(100.0 %)	-	4027(100.0 %)	-	-	-	-
Total	4027	4027	4027	4027	4027	4027	4027	4027	4027

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 29 and to Table 2 on Page 147.

Telithromycin ($MIC_{99.1} \leq 1$ µg/mL, n = 3,390) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 128$ µg/mL, n = 4,027) and clarithromycin ($MIC_{100} \leq 64$ µg/mL, n = 4,027), and the azalide, azithromycin ($MIC_{100} \leq 128$ µg/mL, n = 4,027) agents when tested against 4,027 penicillin-resistant *Streptococcus pneumoniae* (PRSP) isolates.

TABLE 13* shows the MIC distribution (cumulative) to selected antibiotics when testing 340 strains of penicillin-resistant *Streptococcus pneumoniae* (PRSP) for PROTEKT protocol(s) 2000, US and 2001 for outpatients. The resistant breakpoint for penicillin versus *S. pneumoniae* is ≥ 2.0 µg/mL.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae [PEN-R]									
0.008	49 (14.4 %)	-	-	-	-	-	-	-	-
0.015	114 (33.5 %)	-	-	-	-	-	-	-	-
0.03	152 (44.7 %)	-	4 (1.2 %)	55 (16.2 %)	1 (0.3 %)	2 (0.6 %)	-	-	-
0.06	215 (63.2 %)	-	80 (23.5 %)	82 (24.1 %)	9 (2.6 %)	151 (44.4 %)	-	-	-
0.12	266 (78.2 %)	-	83 (24.4 %)	83 (24.4 %)	79 (23.2 %)	187 (55.0 %)	-	-	-
0.25	291 (85.6 %)	-	84 (24.7 %)	84 (24.7 %)	84 (24.7 %)	189 (55.6 %)	-	-	16 (4.7 %)
0.5	332 (97.6 %)	-	85 (25.0 %)	88 (25.9 %)	-	-	-	133 (39.1 %)	32 (9.4 %)
1	338 (99.4 %)	-	88 (25.9 %)	102 (30.0 %)	87 (25.6 %)	-	-	321 (94.4 %)	95 (27.9 %)
2	339 (99.7 %)	269 (61.5 %)	108 (31.8 %)	142 (41.8 %)	96 (28.2 %)	-	3 (0.9 %)	329 (96.8 %)	108 (32.1 %)
4	-	336 (98.8 %)	159 (46.8 %)	167 (49.1 %)	144 (42.4 %)	202 (59.4 %)	103 (30.3 %)	331 (97.4 %)	159 (46.8 %)
8	340(100.0 %)	340(100.0 %)	182 (53.5 %)	184 (54.1 %)	174 (51.2 %)	340(100.0 %)	312 (91.8 %)	334 (98.2 %)	255 (75.0 %)
16	-	-	185 (54.4 %)	185 (54.4 %)	184 (54.1 %)	-	340(100.0 %)	339 (99.7 %)	296 (87.1 %)
32	-	-	186 (54.7 %)	200 (58.8 %)	185 (54.4 %)	-	-	340(100.0 %)	340(100.0 %)
64	-	-	201 (59.1 %)	340(100.0 %)	199 (58.5 %)	-	-	-	-
128	-	-	340(100.0 %)	-	340(100.0 %)	-	-	-	-
Total	340	340	340	340	340	340	340	340	340

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 29 and to Table 10 on Page 202.

Telithromycin ($MIC_{97.6} \leq 1$ µg/mL, n = 332) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 128$ µg/mL, n = 340) and clarithromycin ($MIC_{100} \leq 64$ µg/mL, n = 340), and the azalide, azithromycin ($MIC_{100} \leq 128$ µg/mL, n = 340), agents when tested against 340 penicillin-resistant *Streptococcus pneumoniae* (PRSP) isolates.

Fluoroquinolone Resistance

TABLE 14* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 154 levofloxacin-resistant isolates of *Streptococcus pneumoniae* recovered in the PROTEKT surveillance program.

Levofloxacin-Resistant *Streptococcus pneumoniae*:

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (LEV-R)									
0.004	1 (0.6 %)	-	-	-	-	-	-	-	-
0.008	18 (11.7 %)	4 (2.6 %)	-	-	-	-	-	-	-
0.015	72 (46.8 %)	21 (13.6 %)	-	1 (0.6 %)	-	-	-	-	-
0.03	99 (64.3 %)	30 (19.5 %)	6 (3.9 %)	51 (33.1 %)	2 (1.3 %)	7 (4.5 %)	14 (9.1 %)	-	-
0.06	116 (75.3 %)	65 (42.2 %)	63 (40.9 %)	66 (42.8 %)	17 (11.0 %)	36 (23.4 %)	24 (15.6 %)	-	-
0.12	130 (84.4 %)	68 (44.2 %)	66 (42.9 %)	67 (43.5 %)	62 (40.3 %)	37 (24.0 %)	59 (38.3 %)	-	5 (3.2 %)
0.25	138 (89.6 %)	74 (48.1 %)	-	68 (44.2 %)	65 (42.2 %)	106 (68.8 %)	68 (44.2 %)	-	50 (32.5 %)
0.5	147 (95.5 %)	80 (51.9 %)	68 (44.2 %)	73 (47.4 %)	66 (42.9 %)	107 (69.5 %)	73 (47.4 %)	-	57 (37.0 %)
1	154(100.0 %)	89 (57.8 %)	72 (46.8 %)	78 (50.6 %)	71 (46.1 %)	109 (70.8 %)	78 (50.6 %)	-	66 (42.9 %)
2	-	115 (74.7 %)	79 (51.3 %)	89 (57.8 %)	74 (48.1 %)	123 (79.9 %)	84 (54.5 %)	-	72 (46.8 %)
4	-	154(100.0 %)	91 (59.1 %)	96 (62.3 %)	84 (54.5 %)	125 (81.2 %)	97 (63.0 %)	-	89 (57.8 %)
8	-	-	97 (63.0 %)	104 (67.5 %)	90 (58.4 %)	154(100.0 %)	126 (81.8 %)	53 (34.4 %)	140 (90.9 %)
16	-	-	116 (75.3 %)	117 (76.0 %)	117 (76.0 %)	-	154(100.0 %)	131 (85.1 %)	144 (93.5 %)
32	-	-	117 (76.0 %)	119 (77.3 %)	-	-	-	154(100.0 %)	154(100.0 %)
64	-	-	118 (76.6 %)	154(100.0 %)	118 (76.6 %)	-	-	-	-
128	-	-	154(100.0 %)	-	154(100.0 %)	-	-	-	-
Total	154	154	154	154	154	154	154	154	154

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 30 and to Table 10 on Page 148.

Telithromycin ($MIC_{89.6} \leq 0.25$ µg/mL, n = 138) & telithromycin ($MIC_{95.5} \leq 0.5$ µg/mL, n = 147) is more active than the macrolide, erythromycin A ($MIC_{100} \leq 128$ µg/mL), n = 154) and clarithromycin ($MIC_{100} \leq 64$ µg/mL, n = 154), and the azalide, azithromycin ($MIC_{100} \leq 128$ µg/mL, n = 154), agents when tested against 154 levofloxacin-resistant *Streptococcus pneumoniae* isolates.

In an *in vitro* study[5], 26 quinolone-resistant *Streptococcus pneumoniae* strains from the Alexander Project collection via D. Flemingham and R. Gruneberg, London UK are tested against various antibacterial agents.

TABLE 15* shows the MICs of telithromycin and quinolones and topoisomerase II mutations in the 26 quinolone resistant *Streptococcus pneumoniae* strains.

Quinolone-Resistant *Streptococcus pneumoniae*:

Strain	MIC in µg/ml of							Mutation in QRDR of			
	Pen G	Clarith	Telith	Cipro	Levo	Spar	Moxi	ParC	ParE	GyrA	GyrB
1 (1055)	2.0	16.0	0.03	8.0	8.0	4.0	2.0	S79-F K137-N	I460-V	S81-F	None
2 (1065)	≤0.016	≤0.03	0.016	8.0	2.0	0.5	0.25	S79-Y	I460-V	None	None
3 (1070)	1.0	4.0	0.016	16.0	8.0	1.0	2.0	D83-N	I460-V	S81-F	None
4 (1071)	2.0	≤0.03	0.004	16.0	8.0	1.0	2.0	S79-F K137-N	I460-V	S81-F	None
5 (1073)	≤0.016	≤0.03	≤0.002	8.0	8.0	1.0	1.0	R95-C	D435-N	S81-F	None
6 (1068)	1.0	8.0	0.004	32.0	32.0	8.0	4.0	S79-Y K137-N	I460-V	E85-K	None
7 (1144)	0.03	0.06	0.016	8.0	2.0	1.0	0.25	None	I460-V	None	None
8 (1145)	≤0.016	≤0.03	0.03	8.0	1.0	1.0	0.125	S79-Y	None	None	None
9 (1149)	0.06	2.0	0.5	16.0	4.0	2.0	0.25	S79-Y	None	None	None
10 (1150)	≤0.016	≤0.03	0.016	16.0	8.0	4.0	1.0	S79-F	I460-V	S81-C	None
11 (1151)	4.0	2.0	0.06	16.0	4.0	4.0	0.25	S79-F	I460-V	S81-F	None
12 (1058)	2.0	≤0.03	0.016	8.0	4.0	8.0	0.25	S79-F K137-N	I460-V	None	E474-K
13 (1059)	1.0	≤0.03	0.016	16.0	8.0	8.0	2.0	S79-F K137-N	I460-V	S81-F	None
14 (1060)	2.0	≤0.03	0.008	16.0	8.0	8.0	1.0	S79-F K137-N	I460-V	S81-F	None
15 (1066)	≤0.016	≤0.03	0.016	64.0	16.0	8.0	2.0	S79-F	I460-V	S81-F	None
16 (1076)	≤0.016	>32.0	2.0	32.0	8.0	8.0	1.0	D83-N	None	S81-F	None
17 (1078)	≤0.016	≤0.03	0.004	64.0	16.0	8.0	2.0	S79-F	I460-V	S81-F	None
18 (1156)	0.125	≤0.03	0.016	32.0	16.0	8.0	4.0	S79-F	I460-V	S81-F	None
19 (1074)	≤0.016	≤0.03	0.004	32.0	16.0	8.0	2.0	S79-F K137-N	I460-V	S81-F	None
20 (1077)	≤0.016	≤0.03	0.016	64.0	16.0	8.0	2.0	S79-F	I460-V	S81-Y	None
21 (1135)	1.0	≤0.03	≤0.002	64.0	8.0	8.0	1.0	S79-Y	None	S81-A	None
22 (1139)	1.0	≤0.03	≤0.002	16.0	8.0	16.0	1.0	S79-F K137-N	I460-V	S81-F	None
23 (1146)	2.0	2.0	0.25	32.0	8.0	16.0	2.0	D83-G N91-D	None	S81-F	None
24 (1062)	≤0.016	≤0.03	0.016	64.0	16.0	>32.0	2.0	S79-F	None	S81-Y	None
25 (1072)	≤0.016	>32.0	0.06	32.0	16.0	>32.0	2.0	S79-Y	I460-V	S81-F	None
26 (1147)	4.0	2.0	0.125	64.0	16.0	>32.0	2.0	D83-G N91-D	None	S81-F S114-G	None

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Review Reference 4.

Pen G = penicillin G, Clarith = clarithromycin, Telith = telithromycin, Cipro = ciprofloxacin, Levo =levofloxacin, Spar =sparfloxacin, and Moxi = moxifloxacin.
QRDR = quinolone-resistance determining region.

At this time, there are no FDA approved susceptibility breakpoints for ciprofloxacin when tested against *Streptococcus pneumoniae* isolates. The Applicant decided to use a resistant breakpoint MIC ≥ 8 µg/mL, since they believe this breakpoint is considered highly resistant for this study.

Telithromycin yielded low MICs for all except 1 strain (#16, Strain 1076, MIC = 2.0 µg/mL). Strain 1076 carried an *erm*B gene. The other antibacterials usually yielded higher MICs.

Multiply Drug Resistance

pen-R, ery-R, cot-R, and tet-Resistant *Streptococcus pneumoniae*:

TABLE 16* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 1,500 isolates of *Streptococcus pneumoniae* recovered in the

PROTEKT surveillance program resistant to penicillin G, erythromycin A, trimethoprim/sulfamethoxazole, and tetracycline. It is likely that these isolates are subsets of those previously described when discussing telithromycin susceptibility of *S. pneumoniae* resistant to individual resistant determinants.

	HMR 3647	Penicillin G	Erythromycin A	Clarithromycin	Azithromycin	Clindamycin	Cefuroxime	Levofloxacin	Cotrimoxazole
S.pneumoniae (PEN-R & ERY-R & COT-R & TET-R)									
0.008	10 (0.7 %)	-	-	-	-	-	-	-	-
0.015	123 (8.2 %)	-	-	-	-	-	-	-	-
0.03	345 (23.0 %)	-	-	-	-	5 (0.3 %)	-	-	-
0.06	563 (37.5 %)	-	-	-	-	117 (7.8 %)	-	-	-
0.12	956 (63.7 %)	-	-	-	-	131 (8.7 %)	-	-	-
0.25	1109 (73.9 %)	-	-	-	-	570 (38.0 %)	-	-	-
0.5	1230 (82.0 %)	-	-	7 (0.5 %)	-	578 (38.5 %)	-	284 (19.1 %)	-
1	1491 (99.4 %)	-	7 (0.5 %)	53 (3.5 %)	4 (0.3 %)	591 (38.7 %)	1 (0.1 %)	1433 (95.5 %)	-
2	1497 (99.8 %)	829 (55.3 %)	70 (4.7 %)	356 (23.7 %)	31 (2.1 %)	1193 (73.5 %)	23 (1.5 %)	1462 (97.5 %)	-
4	1499 (99.9 %)	1452 (96.8 %)	359 (23.9 %)	509 (33.9 %)	205 (13.7 %)	1167 (73.8 %)	600 (40.0 %)	1465 (97.7 %)	614 (40.9 %)
8	1500 (100.0 %)	1500 (100.0 %)	513 (34.2 %)	585 (37.0 %)	460 (30.7 %)	1500 (100.0 %)	1327 (88.5 %)	1474 (98.3 %)	1363 (90.9 %)
16	-	-	1084 (72.9 %)	1053 (72.8 %)	1091 (72.7 %)	-	1500 (100.0 %)	1485 (99.7 %)	1431 (95.4 %)
32	-	-	1095 (73.0 %)	1099 (73.3 %)	1094 (72.9 %)	-	-	1500 (100.0 %)	1500 (100.0 %)
64	-	-	1099 (73.3 %)	1500 (100.0 %)	1097 (73.1 %)	-	-	-	-
128	-	-	1500 (100.0 %)	-	1500 (100.0 %)	-	-	-	-
Total	1500	1500	1500	1500	1500	1500	1500	1500	1500

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 31 and to Table 2 on Pg. 148.

TABLE 16* (con't)

	Tetracycline
S.pneumoniae (PEN-R & ERY-R & COT-R & TET-R)	
8	978 (65.2 %)
16	74 (4.9 %)
32	448 (29.9 %)
Total	1500

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 31 and to Table 1, on Page 143.

Cotrimoxazole = Trimethoprim/sulfamethoxazole combination drug product marketed in France.

Telithromycin ($MIC_{99.4}$ ≤1 µg/mL, n = 1,491) is more active than the penicillin G ($MIC_{96.8}$ ≤ 4 µg/mL, n = 1,452), erythromycin A (MIC_{100} ≤ 128 µg/mL, n = 1,500), trimethoprim/sulfamethoxazole ($MIC_{90.9}$ ≤ 8 µg/mL, n = 1,363), and tetracycline (MIC_{100} ≤ 32 µg/mL, n = 1,500) agents when tested against the aforementioned 1,500 multiply resistant *Streptococcus pneumoniae* isolates. These results are expected since the mechanisms of resistance to the other antimicrobials do not confer cross-resistance to telithromycin. That is, we do not expect cross-resistance between telithromycin and the other antibiotic classes.

Of the aforementioned 1,500 multiply-resistant isolates, 35 also demonstrated resistance to levofloxacin.

Pen-R, ery-R, cot-R, tet-R, and levo-Resistant *Streptococcus pneumoniae*:

TABLE 17* shows the telithromycin MICs against 35 multiply drug-resistant isolates from the aforementioned 1,500 isolates of *Streptococcus pneumoniae* recovered in the PROTEKT surveillance program resistant to penicillin G, erythromycin A, trimethoprim/sulfamethoxazole, tetracycline, and now resistant to levofloxacin..

	HMR 3647	Pani-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (PEN-R & ERY-R & COT-R & TET-R & LEV-R)									
0.03	11 (31.4 %)	-	-	-	-	2 (5.7 %)	-	-	-
0.06	21 (60.0 %)	-	-	-	-	10 (28.6 %)	-	-	-
0.12	26 (74.3 %)	-	-	-	-	-	-	-	-
0.25	29 (82.9 %)	-	-	-	-	17 (48.6 %)	-	-	-
0.5	30 (85.7 %)	-	-	2 (5.7 %)	-	-	-	-	-
1	35(100.0 %)	-	1 (2.9 %)	5 (14.3 %)	2 (5.7 %)	-	-	-	-
2	-	14 (40.0 %)	7 (20.0 %)	12 (34.3 %)	4 (11.4 %)	22 (62.9 %)	1 (2.9 %)	-	-
4	-	35(100.0 %)	13 (37.1 %)	15 (42.9 %)	11 (31.4 %)	-	5 (14.3 %)	-	9 (25.7 %)
8	-	-	15 (42.9 %)	17 (48.6 %)	13 (37.1 %)	35(100.0 %)	23 (65.7 %)	9 (25.7 %)	26 (74.3 %)
16	-	-	22 (62.9 %)	22 (62.9 %)	22 (62.9 %)	-	35(100.0 %)	30 (85.7 %)	29 (82.9 %)
32	-	-	-	-	-	-	-	35(100.0 %)	35(100.0 %)
64	-	-	-	35(100.0 %)	-	-	-	-	-
128	-	-	35(100.0 %)	-	35(100.0 %)	-	-	-	-
Total	35	35	35	35	35	35	35	35	35

* Adopted from NDA 21-144, EDR Dated 07/24/02, Table 2 on Pg. 148.

TABLE 17* (con't)

	Tetracycline
S.pneumoniae (PEN-R & ERY-R & COT-R & TET-R & LEV-R)	
8	15 (42.9 %)
16	8 (22.9 %)
32	12 (34.3 %)
Total	35

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table 1, on Page 143.

Cotrimoxazole = Trimethoprim/sulfamethoxazole combination drug product marketed in France.

Telithromycin ($MIC_{100} \leq 1$ µg/mL, n = 35) is more active than the penicillin G ($MIC_{100} \leq 4$ µg/mL, n = 35), erythromycin A ($MIC_{100} \leq 128$ µg/mL, n = 35), trimethoprim/sulfamethoxazole ($MIC_{100} \leq 32$ µg/mL, n = 35), levofloxacin ($MIC_{100} \leq 32$ µg/mL, n = 35), and tetracycline ($MIC_{100} \leq 32$ µg/mL, n = 35) agents when tested against the aforementioned 35 multiply drug-resistant *Streptococcus pneumoniae* isolates.

From the entire PROTEKT population, 129 *Streptococcus pneumoniae* strains were recovered from outpatients that were resistant to penicillin, the macrolides, trimethoprim/sulfamethoxazole, and tetracycline.

Pen-R, ery-R, cot-R, and tet--Resistant *Streptococcus pneumoniae*:

TABLE 18* shows the telithromycin MICs for the 129 *Streptococcus pneumoniae* strains recovered from outpatients that were resistant to penicillin, the macrolides, trimethoprim/sulfamethoxazole, and tetracycline.

	HMR 3647	Peni-cillin G	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Clindamycin	Cefuroxime	Levo-floxacin	Cotri-moxazole
S.pneumoniae (PEN-R & ERY-R & COT-R & TET-R)									
0.008	1 (0.8 %)	-	-	-	-	-	-	-	-
0.015	25 (19.4 %)	-	-	-	-	-	-	-	-
0.03	49 (38.0 %)	-	-	-	-	1 (0.8 %)	-	-	-
0.06	74 (57.4 %)	-	-	-	-	20 (15.5 %)	-	-	-
0.12	96 (69.8 %)	-	-	-	-	24 (18.6 %)	-	-	-
0.25	97 (75.2 %)	-	-	-	-	25 (19.4 %)	-	-	-
0.5	123 (95.3 %)	-	-	3 (2.3 %)	-	-	-	39 (30.2 %)	-
1	129(100.0 %)	-	3 (2.3 %)	9 (7.0 %)	2 (1.6 %)	-	-	119 (92.2 %)	-
2	-	58 (45.8 %)	8 (6.2 %)	20 (15.5 %)	6 (4.7 %)	-	1 (0.8 %)	123 (95.3 %)	-
4	-	125 (96.9 %)	22 (17.1 %)	23 (17.8 %)	18 (14.0 %)	28 (21.7 %)	29 (22.5 %)	-	29 (22.5 %)
8	-	129(100.0 %)	23 (17.8 %)	-	22 (17.1 %)	129(100.0 %)	105 (81.4 %)	126 (98.1 %)	82 (63.6 %)
16	-	-	-	-	23 (17.8 %)	-	129(100.0 %)	129(100.0 %)	101 (78.3 %)
32	-	-	24 (18.6 %)	28 (21.7 %)	24 (18.6 %)	-	-	-	129(100.0 %)
64	-	-	28 (21.7 %)	129(100.0 %)	27 (20.9 %)	-	-	-	-
128	-	-	129(100.0 %)	-	129(100.0 %)	-	-	-	-
Total	129	129	129	129	129	129	129	129	128

* Adopted from NDA 21-144, EDR Dated 07/24/02, Table 10 on Page 203.

TABLE 18* (con't)

	Tetracycline
S.pneumoniae (PEN-R & ERY-R & COT-R & TET-R)	
8	2 (1.6 %)
16	23 (17.8 %)
32	129(100.0 %)
Total	129

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table 10, on Page 207.

Cotrimoxazole = Trimethoprim/sulfamethoxazole combination drug product marketed in France.

Telithromycin ($MIC_{95.3} \leq 0.5$ µg/mL, n = 123) is more active than the penicillin G ($MIC_{96.9} \leq 4$ µg/mL, n = 125), macrolide (erythromycin A ($MIC_{100} \leq 128$ µg/mL, n = 129), and clarithromycin ($MIC_{100} \leq 64$ µg/mL, n = 129), trimethoprim/sulfamethoxazole ($MIC_{100} \leq 32$ µg/mL, n = 129), and tetracycline ($MIC_{100} \leq 32$ µg/mL, n = 129) agents when tested against the aforementioned 129 multiply drug-resistant *Streptococcus pneumoniae* isolates.

Haemophilus influenzae:

TABLE 19* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 8,064 isolates of *Haemophilus influenzae* recovered in the PROTEKT surveillance program.

	HMR 3647	Erythromycin A	Clarithromycin	Azithromycin	Cefuroxime	Cotrimoxazole	Ampicillin	Tetracycline
H.influenzae								
0.002	6 (0.1 %)	-	-	-	-	-	-	-
0.008	7 (0.1 %)	-	-	-	-	-	-	-
0.015	8 (0.1 %)	-	-	-	-	-	-	-
0.03	14 (0.2 %)	-	-	-	-	2016 (37.6 %)	-	-
0.06	43 (0.5 %)	-	-	26 (0.3 %)	-	4007 (74.8 %)	-	8 (0.1 %)
0.12	83 (1.0 %)	-	-	108 (1.3 %)	122 (1.5 %)	4292 (80.1 %)	1950 (24.7 %)	110 (1.4 %)
0.25	183 (2.3 %)	30 (0.6 %)	34 (0.4 %)	339 (4.2 %)	667 (8.3 %)	4346 (81.1 %)	3634 (45.1 %)	1013 (12.6 %)
0.5	1521 (18.9 %)	62 (1.2 %)	59 (0.7 %)	1715 (21.3 %)	4077 (50.6 %)	4360 (81.4 %)	5918 (73.4 %)	5988 (86.7 %)
1	4892 (60.7 %)	171 (3.2 %)	100 (1.2 %)	5478 (67.8 %)	6731 (83.5 %)	4401 (82.1 %)	6341 (78.6 %)	7837 (97.2 %)
2	7439 (92.2 %)	1037 (19.4 %)	336 (4.2 %)	7534 (93.4 %)	7587 (94.1 %)	4517 (84.3 %)	6417 (79.6 %)	7860 (97.5 %)
4	7958 (98.7 %)	4340 (81.0 %)	1859 (23.1 %)	7988 (99.2 %)	7929 (98.3 %)	4934 (92.1 %)	6484 (80.4 %)	7896 (97.9 %)
8	8048 (99.8 %)	5297 (98.9 %)	6428 (79.7 %)	8041 (99.7 %)	8036 (99.7 %)	5348 (97.9 %)	7295 (90.5 %)	7971 (98.8 %)
16	8064 (99.9 %)	5343 (99.7 %)	7835 (97.2 %)	8053 (99.9 %)	8052 (99.9 %)	5351 (99.9 %)	7439 (92.2 %)	8040 (99.7 %)
32	8064 (100.0 %)	5350 (99.9 %)	8025 (99.5 %)	8064 (100.0 %)	8060 (100.0 %)	5358 (100.0 %)	8064 (100.0 %)	8064 (100.0 %)
64	-	5354 (99.9 %)	8058 (99.9 %)	-	8064 (100.0 %)	-	-	-
128	-	5358 (100.0 %)	8064 (100.0 %)	-	-	-	-	-
ND	-	2706	-	-	-	2706	-	-
Total	8064	8064	8064	8064	8064	8064	8064	8064

* Adopted from NDA 21-144, EDR Dated 07/24/02, Page 36 (refer to Table 30 on Page 346).

Telithromycin ($MIC_{92.2} \leq 2$ µg/mL, n = 7,439) and the azalide, azithromycin ($MIC_{93.4} \leq 2$ µg/mL, n = 7,534) are more active than the macrolides, erythromycin A ($MIC_{98.9} \leq 8$ µg/mL, n = 5,297) and clarithromycin ($MIC_{97.2} \leq 16$ µg/mL, n = 7,835) against the 8,064 *Haemophilus influenzae* isolates. As a point of reference, the azithromycin and clarithromycin susceptible breakpoints are 4.0 µg/mL and 8.0 µg/mL. Thus, 99.2 and 79.7% of the isolates are susceptible to azithromycin and clarithromycin, respectively.

Haemophilus influenzae (β-lactamase producers):

TABLE 20* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 1,631 β-lactamase producing strains of *Haemophilus influenzae* recovered in the PROTEKT surveillance program.

	HMR 3647	Erythromycin A	Clarithromycin	Azithromycin	Cefuroxime	Cotrimoxazole	Ampicillin	Tetracycline
H.influenzae (beta-lactamase producer)								
0.008	1 (0.1 %)	-	-	-	-	-	-	-
0.015	2 (0.1 %)	-	-	-	-	-	-	-
0.03	-	-	-	-	-	318 (36.9 %)	-	-
0.06	5 (0.3 %)	-	-	3 (0.2 %)	-	578 (67.1 %)	-	1 (0.1 %)
0.12	14 (0.9 %)	-	-	18 (1.1 %)	16 (1.0 %)	605 (70.2 %)	-	15 (0.9 %)
0.25	25 (1.5 %)	2 (0.2 %)	7 (0.4 %)	47 (2.9 %)	121 (7.4 %)	619 (71.8 %)	-	180 (11.0 %)
0.5	206 (12.6 %)	8 (0.9 %)	13 (0.8 %)	260 (15.9 %)	827 (50.7 %)	622 (72.2 %)	-	1335 (81.9 %)
1	783 (48.0 %)	21 (2.4 %)	18 (1.1 %)	1001 (61.4 %)	1351 (83.0 %)	626 (72.6 %)	-	1462 (89.6 %)
2	1419 (88.2 %)	128 (14.8 %)	58 (3.6 %)	1485 (91.0 %)	1544 (94.7 %)	646 (74.9 %)	12 (0.7 %)	1471 (90.2 %)
4	1606 (98.5 %)	673 (78.1 %)	278 (17.0 %)	1613 (98.9 %)	1610 (98.7 %)	733 (85.0 %)	71 (4.4 %)	1501 (92.0 %)
8	1627 (99.8 %)	854 (99.1 %)	1203 (73.8 %)	1628 (99.8 %)	1628 (99.9 %)	817 (94.8 %)	852 (52.9 %)	1561 (95.7 %)
16	1631 (100.0 %)	859 (99.7 %)	1563 (95.8 %)	1631 (100.0 %)	1630 (99.9 %)	860 (89.8 %)	1006 (61.7 %)	1610 (98.7 %)
32	-	860 (99.8 %)	1620 (99.3 %)	-	1631 (100.0 %)	862 (100.0 %)	1631 (100.0 %)	1631 (100.0 %)
64	-	862 (100.0 %)	1630 (99.9 %)	-	-	-	-	-
128	-	-	1631 (100.0 %)	-	-	-	-	-
ND	-	769	-	-	-	769	-	-
Total	1631	1631	1631	1631	1631	1631	1631	1631

* Adopted from NDA 21-144, EDR Dated 07/24/02, Page 36 (refer to Table 30 on Page 346).

Telithromycin, $MIC_{88.2} \leq 2$ µg/mL (n = 1,439) and $MIC_{98.5} \leq 4$ µg/mL (n = 1,606), is the most active of the related macrolides tested against the 1,631 β-lactamase producing strains of *Haemophilus influenzae* recovered in the PROTEKT surveillance program. A comparison of telithromycin MICs of β-lactamase positive and β-lactamase negative *H. influenzae* suggests that the MIC_{50} increase

from 1.0 µg/mL to 2.0 µg/mL in β-lactamase positive isolates. The MIC_{90} increases one tube dilution from 2.0 µg/mL to 4.0 µg/mL. It is not clear why this increase is noted since the mode of action of β-lactam antimicrobials and ketolides differs.

Moraxella catarrhalis:

Over 90% of all isolates of *M. catarrhalis*, a common respiratory tract pathogen, produce β-lactamases that renders them resistant to compounds such as amoxicillin. Data presented in the original telithromycin NDA indicated that telithromycin exhibits equal or superior activity to clarithromycin. *In vitro* studies conducted subsequently support those initial findings.

TABLE 21* shows the comparative *in vitro* activities of antibacterial agents commonly prescribed for the treatment of RTIs against 1,071 β-lactamase producing strains of *Moraxella catarrhalis* recovered in the PROTEKT 2000 surveillance program.

	HMR 3647	Erythro-mycin A	Clari-thromycin	Azi-thromycin	Cefuroxime	Cotri-moxazole	Ampicillin	Tetracycline
M.catarrhalis (beta-lactamase producer)								
0.008	3 (0.3 %)	-	-	-	-	-	-	-
0.015	6 (0.6 %)	-	-	-	-	-	-	-
0.03	83 (7.7 %)	-	-	-	-	1 (0.1 %)	-	-
0.06	786 (73.4 %)	-	-	1068 (99.8 %)	-	90 (8.4 %)	-	-
0.12	1032 (96.4 %)	-	-	1070 (99.9 %)	-	499 (46.6 %)	2 (0.2 %)	35 (3.3 %)
0.25	1069 (99.8 %)	1014 (94.7 %)	1063 (99.3 %)	1071(100.0 %)	10 (0.9 %)	937 (87.5 %)	9 (0.8 %)	910 (85.0 %)
0.5	1071(100.0 %)	1067 (99.6 %)	1071(100.0 %)	-	228 (21.3 %)	1046 (97.7 %)	34 (3.2 %)	1052 (98.2 %)
1	-	1071(100.0 %)	-	-	628 (57.9 %)	1062 (99.2 %)	87 (8.1 %)	1053 (98.3 %)
2	-	-	-	-	988 (92.3 %)	1069 (99.8 %)	202 (18.9 %)	-
4	-	-	-	-	1057 (98.7 %)	1071(100.0 %)	410 (38.3 %)	1056 (98.4 %)
8	-	-	-	-	1071(100.0 %)	-	766 (71.5 %)	1061 (99.1 %)
16	-	-	-	-	-	-	1027 (95.9 %)	1065 (99.4 %)
32	-	-	-	-	-	-	1071(100.0 %)	1071(100.0 %)
Total	1071	1071	1071	1071	1071	1071	1071	1071

* Adopted from NDA 21-144, EDR Dated 07/24/02, Page 37 (refer to Table 32 on Page 351).

The azalide, azithromycin ($MIC_{99.8} \leq 0.06$ µg/mL, n = 1,069), is the most active tested against the 1,071 β-lactamase producing strains of *Moraxella catarrhalis* recovered in the PROTEKT surveillance program. The ketolide, telithromycin ($MIC_{96.4} \leq 0.12$ µg/mL, n = 1,032), is the 2nd most active. The macrolide results are: erythromycin ($MIC_{94.7} \leq 0.25$ µg/mL, n = 1,014), and clarithromycin ($MIC_{99.3} \leq 0.25$ µg/mL (n = 1,063).

Atypical Pathogens

Mycoplasma pneumoniae (extracellular; however, possibly some intracellular):

TABLE 22* shows the comparative *in vitro* activities of telithromycin and other antimicrobial agents against 25 isolates *Mycoplasma pneumoniae*.

	MIC (mg/L)		
Antimicrobial	MIC_{50}	MIC_{90}	range
Telithromycin	≤0.015	≤0.015	≤0.015
Erythromycin	≤0.015	≤0.015	≤0.015
Roxithromycin	≤0.015	≤0.015	≤0.015–0.03
Dirithromycin	≤0.015	≤0.015	≤0.015–0.06
Clarithromycin	≤0.015	≤0.015	≤0.015
Azithromycin	≤0.015	≤0.015	≤0.015
Josamycin	≤0.015	0.03	≤0.015–0.03
Levofloxacin	0.5	1	0.5–1
Ofloxacin	1	1	1
Spiramycin	0.06	0.25	≤0.015–0.25
Doxycycline	0.12	0.25	0.06–0.25

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 38 and to Review Reference 5.

Telithromycin (MIC_{90} ≤ 0.015 mg/mL) and the related macrolides have similar activity against the 25 *Mycoplasma pneumoniae* isolates.

Chlamydia pneumoniae (intracellular):

TABLE 23* shows the comparative *in vitro* activities of telithromycin and macrolides against 19 isolates of *Chlamydia pneumoniae*.

	MIC (mg/L)			MBC (mg/L)	
Antimicrobial	MIC_{50}	MIC_{90}	range	MBC_{90}	range
Telithromycin	0.0625	0.25	0.031–2	0.25	0.031–2
Roxithromycin	0.25	0.5	0.0625–2	0.5	0.0625–2
Erythromycin	0.125	0.25	0.015–0.25	0.25	0.0625–0.5
Azithromycin	0.125	0.25	0.015–0.5	0.25	0.015–0.5

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 39 and to Reference 6.

The ketolide, Telithromycin (MIC_{90} = 0.25 mg/L), and the macrolide, erythromycin (MIC_{90} = 0.25 mg/L), and the azalide, azithromycin (MIC_{90} = 0.25 mg/L), all have similar activity against the 19 *Chlamydia pneumoniae* isolates.

Legionella pneumophila (intracellular):

TABLE 24* shows the MIC distributions for antibacterial agents with activity against 26 *Legionella pneumophila* isolates PROTEKT 2000).

	No. (%) of strains at each MIC for specified antibiotic						
MIC (µg/mL)	TEL	ERY A	CLA	AZI	LVF	COT	TET
L. pneumophila							
≤0.004	7 (26.9)	-	-	-	-	-	-
0.008	12 (46.2)	-	-	-	23 (88.5)	-	-
0.015	7 (26.9)	-	-	-	3 (11.5)	-	-
0.06	-	-	-	25 (96.2)	-	-	-
0.12	-	-	-	1 (3.8)	-	2 (7.7)	-
0.25	-	25 (96.2)	26 (100)	-	-	14 (53.8)	-
0.5	-	1 (3.8)	-	-	-	10 (38.5)	-
≥32	-	-	-	-	-	-	26 (100)
ND	-	-	-	-	-	-	-
Total	26	26	26	26	26	26	26

* Adopted from NDA 21-144, EDR Dated 07/24/02, refer to Table on Page 40 and to Reference 7.

TEL: telithromycin, ERY A: erythromycin A, CLA: clarithromycin, AZI: azithromycin, LVF: levofloxacin, COT: cotrimoxazole, and TET: tetracycline; - = No isolates at this MIC.

Telithromycin (MIC_{100} ≤ 0.015 µg/mL) is the most active compared to the macrolide, erythromycin A ($MIC_{96.2}$ ≤ 0.25 µg/mL), and the azalide, azithromycin ($MIC_{96.2}$ ≤ 0.06 µg/mL) tested against the 26 *Legionella pneumophila* isolates. It is a well-established fact that macrolide antimicrobial drugs concentrate at higher levels intracellularly than levels found in blood. The same characteristic is noted for telithromycin.

TABLE 25: CLINICAL MICROBIOLOGIST'S SUMMARY OF *IN VITRO* DATA

Microorganism	Study	Number Isolates	MIC (%-Susceptibe)	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

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

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
Haemophilus influenzae	2,706	96.2	4
	8,064	92.2	2
β-lact +	1,631	88.2	2
Streptococcus pyogenes	3,918	95	0.03
Moraxella catarrhalis	1,071	99.8	0.06
Mycoplasma pneumoniae	25	90	0.015
Chlamydia pneumoniae	19	90	0.25
Legionella pneumophila	26	100	0.015

MISCELLANEOUS STUDIES

CO_2 Effect:

The Applicant submitted new information on the effect of 5% to 6% CO_2 on MICs for *Haemophilus influenzae and Streptococcus pneumoniae* isolates.

TABLE 26* Telithromycin: MIC determinations against *H. influenzae* and *S. pneumoniae* under 6% CO2 atmosphere.

			TEL MIC (µg/mL)		
	Atmosphere	N	50	90	Range
H, influenzae β-lactamase-ve	Ambient air	20	1.0	2.0	0.5–2.0
H, influenzae β-lactamase-ve	6% CO_2	20	2.0	4.0	1.0–8.0
H, influenzae β-lactamase+ve	Ambient air	24	1.0	2.0	0.15–2.0
H, influenzae β-lactamase+ve	6% CO_2	24	2.0	4.0	1.0–4.0
S. pneumoniae Pen-R, ery-R	Ambient air	23	0.03	0.25	0.008–0.5
S. pneumoniae Pen-R ery-R	6% CO_2	23	0.25	2.0	0.03–2.0

*Adopted from NDA 21-144, EDR Dated 07/24/02, Table on Page 60

TEL: telithromycin, -ve: negative, +ve: positive.

Clinical Microbiologist's Comments:

It was demonstrated that incubation in 6% CO_2 results in approximately a 2-fold increase in telithromycin MIC values against *Streptococcus pneumoniae* and *Haemophilus influenzae*.

III. PRECLINICAL EFFICACY (*IN VIVO*)

Pharmacokinetics and Pharmacodynamics

Animal Studies

Concentration-dependent bactericidal activity of telithromycin versus time-dependent activity for erythromycin and clarithromycin

AUC/MIC is the major PK/PD parameter determining the efficacy of both telithromycin and azithromycin in murine infection models. In a recent study, the neutropenic murine thigh-infection model was employed to determine whether there are differences between the two compounds in the pattern of bacterial killing against strains of *Streptococcus pneumoniae*. The two compounds

were shown to differ markedly in their *in vivo* killing characteristics. Telithromycin exhibits concentration-dependent killing significantly greater with telithromycin than with azithromycin. The concentration-dependent killing of telithromycin was shown to extend from erythromycin A susceptible strains to organisms resistant to erythromycin A both because of efflux (expression of *mef*A genome) and methylation at the A-2058 moiety of domain V of the 23S rRNA (expression of *erm*B. The investigators concluded that the rapid rate of killing of telithromycin against *Streptococcus pneumoniae* might allow the compound to be effective using a shorter duration of therapy.

The applicant did not provide an analysis of the pharmacodynamics of telithromycin, which will aid in the determination of the final interpretative criteria. The following deficiency should be conveyed to the applicant.

Deficiency:

The following comments pertain to the clinical microbiology of telithromycin:

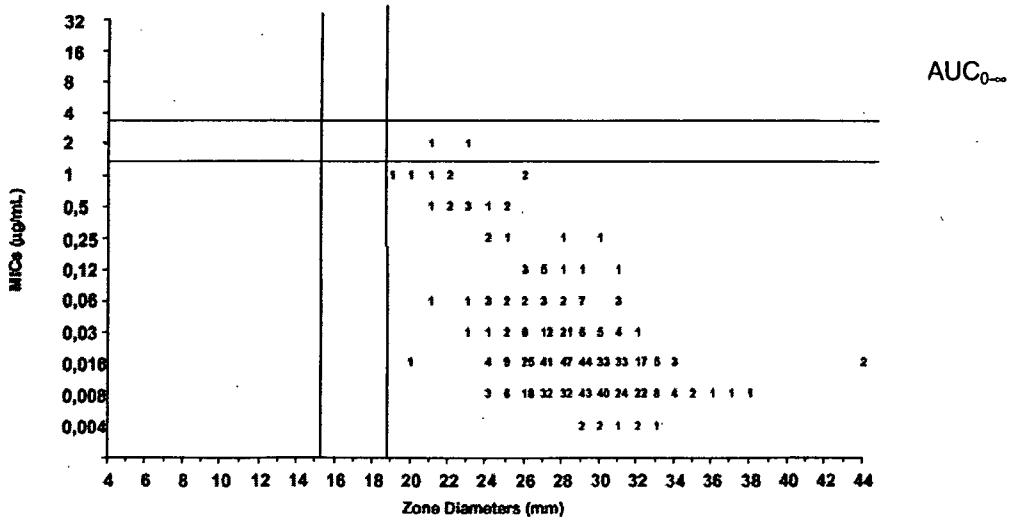
- Submit an analysis of the pharmacodynamics (PD) of telithromycin when dosed as directed in health adults and patients.
- Studies have shown that the microbiological activity of telithromycin is concentration dependent and the appropriate PD parameter is the AUC/MIC ratio. This information is of interest in determining appropriate interpretative criteria.
- Provide a PD analysis using AUC/MIC_{90} ratios for *Streptococcus pneumoniae, Haemophilus influenzae*, and *Staphylococcus aureus*. The analysis should include total populations and subset analysis with pathogens having desired antibiotic resistance determinants. Perform the analysis using total and free telithromycin drug concentrations. The origin of the data should be clearly identified.

In the following Table 28, in the PK assessments in Healthy Subjects, Study #1008, "Elimination Kinetics", under Multiple doses: the Cmax (mg/L) = 2.27 (31) and the range = [redacted] / mg/L. The $AUC_{0-\infty}$ (mg/h/L) = 12.5 (43). Using Dr. Craig's theory that ≥ 20 to 50 is an ideal range, then Dr. Marsik's original proposed breakpoint for *Streptococcus pneumoniae* is reasonable and acceptable [redacted]

Human Studies:

TABLE 27 is a Summary of the Pharmacokinetics of Telithromycin (adapted from Jenny J. Zheng, Ph.D., HFD-880/Biopharmaceutics, Completed 05/31/02).

PK Assessments in Healthy Subjects	PK Parameters After 800 mg QD (Unless Noted) Expressed as Mean (CV)
Absorption and Systemic Bioavailability (Study 1044)	Tablet Absolute Bioavailability: Young: 57.3 (31); Elderly 56.6 (20) T_{max}: 2.5 –3 hours
Food Effects (Study 1003)	None
Distribution	Protein Binding: 60% – 70% Bound V_{ss} (L): Young subjects:210 (27); elderly subjects: 226 (21) Penetration into tissues: Blister fluid/tonsil secretion/pulmonary tissue/saliva
Metabolism (Study 1009)	Mainly metabolized (22% and 12% unchanged in feces and urine) CYP3A substrate Four metabolites have been identified.
Excretion (Study 1009)	Urine: 12% recovered as unchanged telithromycin Feces: 22% recovered as unchanged telithromycin
Elimination Kinetics (Study 1008)	Single dose: C_{max} (mg/L)= 1.90 (42); range:0.964-3.252 $AUC_{0-\infty}$(mg*h/L)= 8.25 (31) $t_{1/2}$ (h): 7.16 (19) CL/F (L/h): 102.3 (31) range: 53.5-184.8 CLr/F_{0-24}: (L/h): 12.32 (17) Multiple doses: C_{max} (mg/L)= 2.27(31); range:1.40-3.77 mg/L $AUC_{0-\infty}$(mg*h/L)= 12.5 (43); range: 7.08-31.53 $t_{1/2}$ (h): 9.81 (20) CL/F (L/h): 71.1 (29) range: 25.4-85.2 CLr/F: (L/h): 12.5 (34)
Disposition Kinetics	Nonlinear pharmacokinetics Slightly more than dose proportional Increases in AUC and C_{max} after 400 mg, 800 mg and 1600 mg. Accumulation was about 1.5 after multiple doses.
Significant Interactions	CYP3A4 inhibitor: ↑ telithromycin by ketoconazole/intraconazole ↔ telithromycin by grapefruit juice CYP3A4 substrate: ↑ cisapride /↑ simvastatin/↑ midazolam CYP2D6 substrate: ↔paroxetine CYP1A2 substrate: ↑ theophylline CYP2C9 substrate: ↔ warfarin Others: ↑ digoxin / ↔ oral contraceptive (ethinylestradiol)/ ↓ sotalol Gastric pH: telithromycin not changed by ranitidine and Maalox
Renal impairment	AUC and C_{max} were increased in both moderate and severe renal impaired subjects after single dose.
Hepatic Impairment	AUC and C_{max} are comparable but $t_{1/2}$ ↑ significantly. No dose adjustment recommended by the sponsor.
Effects of Age on PK	AUC and C_{max} increased by 100% after repeat dose but no dose adjustment recommended by the sponsor.
Effects of Gender on PK	None



IV. CLINICAL EFFICACY

Clinical Trials

Community Acquired Pneumoniae (CAP)

The Applicant conducted 2 new multi-national studies for Community Acquired Pneumoniae (CAP), Protocols #3012 and #4003, to provide additional data for *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A (macrolide).

The applicant provided data on a previous Japanese study (Protocol #2105) and a new Japanese Study (Protocol #3107). The studies were considered to be only supportive studies, if at all considered.

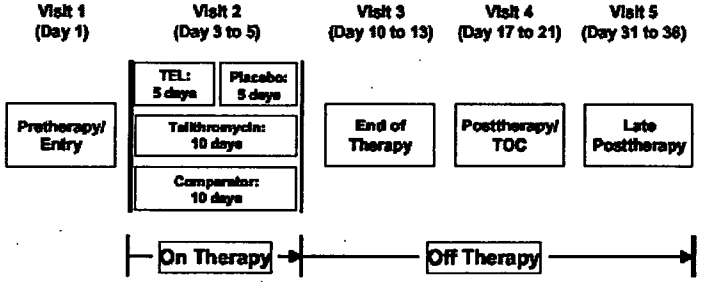
and

Acute Exacerbation of Chronic Bronchitis (AECB)

The Applicant has conducted an additional study in subjects with AECB, Protocol #3107(US), to provide further efficacy data for *Haemophilus influenzae* and *Moraxella catarrhalis* (irrespective of β-lactamase production by either organism).

FIGURE 1. shows a general study design for each indication.

Generalized study design (Phase III clinical studies)



Adopted from NDA 21-144, EDR Dated 07/24/02, on Page 93.

Dosage Regimen:

Telithromycin:

CAP: 7 to 10 days
AECB: 5 days
Acute Sinusitis: 5 and 10 days

TABLE 28* describes the main analysis populations in the clinical studies for determining telithromycin efficacy:

Population	Definition
MITT	All randomized subjects, as treated, with a confirmed diagnosis of infection who received at least 1 dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and X-ray findings, as specified in the protocols. This definition was intended to exclude subjects with a clear misdiagnosis, for whom study medication could have no therapeutic effect.
PPc	All mITT subjects except those with major protocol violations and/or indeterminate responses.
bmITT	All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for infection.
PPb	All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

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* Adopted from NDA 21-144, EDR Dated 07/24/02, Table on Page 94.

The clinical program included 16 trials for the 3 primary indications. One, the Japanese study (Study 3107), was only used for *Streptococcus pneumoniae* isolates that were resistant to erythromycin A and other macrolides, or to penicillin G.

The clinical and bacteriological analyses are done on the Per Protocol$_b$ population (PP_b).

b = bacteriological

All studies were designed according to the FDA "Points to Consider" and the IDSA guidelines. Data from 15 studies were included in all of the assessments. All were international studies, and the FDA-approved protocol was common to all centers.

TABLE 29* shows the clinical studies to support the Applicant's 3-proposed indications.

Indication/study no.	Study design			
CAP				
3000 (Europe)	Open label	7–10 d	TEL	800 mg qd
3001 (Europe)	Double-blind, randomized, active	10 d	TEL	800 mg qd
	controlled, 2-arm, parallel group	10 d	AMX	1000 mg tid
3006 (US)	Double-blind, randomized, active	10 d	TEL	800 mg qd
	controlled, 2-arm, parallel group	10 d	CLA	500 mg bid
3009 (US)	Double-blind, randomized, active	7–10 d	TEL	800 mg qd
	controlled, 2-arm, parallel group	7–10 d	TVA	200 mg qd
3009OL (US)	Open label	7–10 d	TEL	800 mg qd
3010 (US)	Open label	7d	TEL	800 mg qd
3012 (US)	***Open label***	***7 d***	***TEL***	***800 mg qd***
4003 (US)	***Double-blind, randomized, active***	***5 d***	***TEL***	***800 mg qd***
	controlled, 3-arm, parallel group	***7 d***	***TEL***	***800 mg qd***
		10 d	***CLA***	***500 mg bid***
2105 (Japan)	Double-blind, randomized, active	7d	TEL	600 mg qd
	2-arm, parallel group	7d	TEL	800 mg qd
3107 (Japan)	***Double-blind, randomized, active***	***7 d***	***TEL***	***600 mg qd***
	controlled, 2-arms, parallel group	***7 d***	***LEV***	***100 mg tid***
Acute exacerbation of chronic bronchitis				
3003 (Europe)	Double-blind, randomized, active	5 d	TEL	800 mg qd
	controlled, 2-arm, parallel group	10 d	AMC	500 mg/125 mg tid
3007 (US)	Double-blind, randomized, active	5 d	TEL	800 mg qd
	controlled, 2-arm, parallel group	10 d	CXM	500 mg bid
3013 (US)	***Double-blind, randomized, active***	***5 d***	***TEL***	***800 mg qd***
	controlled, 2-arm, parallel group	***10 d***	***CLA***	***500 mg bid***
Acute sinusitis				
3002 (Europe)	Double-blind, randomized, active	5 d	TEL	800 mg qd
	2-arm, parallel group	10 d	TEL	800 mg qd
3005 (US)	Double-blind, randomized, active	5 d	TEL	800 mg qd
	controlled, 3-arm, parallel group	10 d	TEL	800 mg qd
		10 d	AMC	500 mg/125 mg tid
3011 (US)	Double-blind, randomized, active	5 d	TEL	800 mg qd
	controlled, 2-arm, parallel group	10 d	CXM	250 mg bid

* Adopted from NDA 21-144, EDR Dated 07/24/02, Table on Page 95.

Community Acquired Pneumoniae (CAP)

The Applicant conducted 2 new studies for Community Acquired Pneumoniae (CAP), Protocols #3012 and #4003, and 2 (1-old and 1-new) Japanese studies, Protocols #2105 and #3107, to provide additional data for *Streptococcus pneumoniae* isolates resistant to penicillin G (PRSP) and erythromycin A (macrolide).

Clinical CAP Protocol #3012

Title:

Multicenter, open-label, multinational, non-comparative, uncontrolled study of the efficacy and safety of 7 days of oral telithromycin (HMR 3647 800 mg once daily) in the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* in adolescents and adults.

Investigator(s), Study Site(s):

Multicenter study, subjects were enrolled at a total of 68 investigational sites in the following countries: Argentina (9 sites), France (9 sites), Mexico (3 sites), South Africa (17 sites), Spain (4 sites), and the US (26 sites).

-- Study manager:

[redacted]

Indication:

Community-acquired pneumonia (CAP)

Objectives:

-- Primary Objective:

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

-- Secondary Objectives:

To evaluate the clinical and bacteriological efficacy of 7 days of oral telithromycin in the treatment of CAP due to *Streptococcus pneumoniae* in adolescents and adults.

To evaluate the clinical and bacteriological efficacy of 7 days of oral telithromycin in the treatment of CAP in adolescents and adults.

Design:

This was an open-label, multicenter, multinational, uncontrolled, study. Study medication was given daily for 7 days.

There were four visits: a pretherapy/entry visit (Day 1), an on-therapy visit (Days 3 to 5), an end-of-therapy visit (Days 8 to 10), and a posttherapy/test of cure (TOC) visit (Days 17 to 21).

Population:

Adolescent and adult subjects with clinical findings and chest x-ray findings compatible with a diagnosis of CAP, presumably due to *Streptococcus pneumoniae*. Approximately 400 subjects were to be enrolled, with the assumption that approximately 25% of the subjects will have *Streptococcus pneumoniae* isolated and 20-30 subjects will have *Streptococcus pneumoniae* resistant to penicillin G and/or erythromycin A (macrolides) in the bacteriological per protocol (PP_b) population.

Treatment:

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

Efficacy Data:

-- Primary Efficacy Data:

Clinical outcome in the PPc population and bacteriological outcome in the PP_b population at the posttherapy/TOC visit.

-- Secondary Efficacy Data

Clinical outcome in the mITT population and bacteriological outcome in the bmITT population at the posttherapy/TOC visit.

Study Duration and Dates:

The first subject entered the study on 21 February 2001. This study report includes subjects enrolled through 18 January 2002 and who completed the last study visit (posttherapy/TOC) by 22 February 2002. Subjects enrolled after 18 January 2002 will be included in a separate clinical study report to be provided at a later date.

Clinical CAP Protocol #4003

Title:

Multicenter, double-blind, randomized, active-controlled, comparative, 3-arm parallel group study of the efficacy and safety of oral telithromycin (HMR 3647 800 mg once daily) 5 days versus 7 days versus 10 days oral clarithromycin (500 mg twice daily) in the treatment of community-acquired pneumonia (CAP).

Investigator(s), Study Site(s):

Multicenter study conducted at a total of 77 investigational sites in the following countries: Argentina (8 sites), Brazil (5 sites), Canada (14 sites), Chile (2 sites), Germany (6 sites), South Africa (9 sites), Spain (4 sites), United Kingdom (5 sites) and United States (24 sites).

-- Study Manager:

Manish Patel, Pharm D., Aventis Pharmaceuticals, Inc., Parsippany, NJ, United States.

Indication:

Community-acquired pneumonia (CAP)

Objectives:

-- Primary Objective:

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

-- Secondary Objective:

To compare bacteriological efficacy of 5 days and 7 days of oral telithromycin and 10 days of oral clarithromycin for treating CAP due to common or atypical and intracellular pathogens in adults.

Design:

This study was a multicenter, double-blinded, active-controlled, three-arm parallel-group (1:1:1) comparative study of telithromycin (800 mg given once daily) for 5 days versus 7 days versus 10 days of oral clarithromycin (500 mg given twice daily).

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

Population:

Adult subjects with clinical findings and chest x-ray findings compatible with a diagnosis of CAP, presumably due to common or atypical and intracellular bacterial pathogens. Approximately 516 subjects (172 subjects per treatment arm) were to be enrolled, with the goal of obtaining approximately 120 clinically evaluable subjects per treatment arm.

Treatments:

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

Efficacy Data:

-- Primary Efficacy Data:

Clinical outcome at the posttherapy/TOC visit in the PPc population.

-- Secondary Efficacy Data:

Bacteriological outcome at the posttherapy/TOC visit in the PPb population, and clinical and bacteriological outcomes at late posttherapy in the PPc and PPb populations, respectively.

Study Duration and Dates:

The study took place between 29 December 1999 and 20 April 2001.

CAP Clinical Outcome and Bacteriological Outcome Results at TOC

TABLE 30* CAP Protocols: #3012 & #4003 – Per Protocol (PP_b) Population

Continent	Clinical Outcome	Bacteriological Outcome

North America

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

Clinical Outcome	Bacteriological Outcome
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

Clinical Outcome	Bacteriological Outcome
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

Clinical Outcome	Bacteriological Outcome
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 *Haemophilus parainfluenzae* at Baseline = 35

Clinical Outcome	Bacteriological Outcome
Patients Cured = 31/35 (88.6%)	Presumed Eradicated = 27/35 (77.1%)
Patient Failures = 4/35 (11.4%)	Persistence = 6/35 (17.1%)
	Presumed Persistence = 2/35 (05.7%)

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

Clinical Outcome	Bacteriological Outcome
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

Clinical Outcome	Bacteriological Outcome
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

Clinical Outcome	Bacteriological Outcome
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 *Haemophilus parainfluenzae* at Baseline = None.

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

Clinical Outcome	Bacteriological Outcome
Patients Cured = 1/1 (100%)	Recurrence = 1/1 (100%)

TABLE 30* (con't) CAP Protocols: #3012 & #4003 – Per Protocol (PP_b) Population

Continent	Clinical Outcome	Bacteriological Outcome
Europe		
1. Number of patients isolated with *Staphylococcus aureus* at baseline = 5		
	Patients Cured = 4/5 (80%)	Eradication = 1/5 (20%)
	Patients Failed = 1/5 (20%)	Presumed Eradicated = 3/5 (60%)
	Eradication +	Presumed Eradicated = 4/5 (80%)
		Presumed Persistence = 1/5 (20%)
2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 15		
	Patients Cured = 14/15 (93.3%)	Eradicated = = 2/15 (13.3%)
	Patients Failures = 1/15 (6.7%)	Presumed Eradicated = 12/15 (80%)
	Eradication +	Presumed Eradicated = 14/15 (93.3%)
		Presumed Persistence = 1/15 (6.7%)
3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 9		
	Patients Cured = 7/9 (77.8%)	Eradicated = 1/9 (11.1%)
	Patients Failures = 2/9 (22.2%)	Presumed Eradicated = 6/9 (66.7%)
	Eradication +	Presumed Eradicated = 7/9 (77.8%)
4. Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = 3		
	Patients Cured = 3/3 (100%)	Presumed Eradicated = 3/3 (100%)
5. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 5		
	Patients Cured = 5/5 (100%)	Eradicated = 1/5 (20%)
		Presumed Eradicated = 4/5 (80%)
Africa		
1. Number of patients isolated with *Staphylococcus aureus* at baseline = 7		
	Patients Cured = 7/7 (100%)	Eradication = 1/7 (14.3%)
		Presumed Eradicated = 6/7 (85.7%)
	Eradication +	Presumed Eradicated = 7/7 (100%)
2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 89		
	Patients Cured = 84/89 (94.4%)	Eradicated = 16/89 (18%)
	Patients Failures = 5/89 (5.6%)	Presumed Eradicated = 72/89 (80.9%)
	Eradication +	Presumed Eradicated = 88/89 (98.9%)
		Presumed Persistence = 1/89 (1.1%)
3. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 71		
	Patients Cured = 66/71 (93%)	Eradicated = 5/71 (7%)
	Patients Failures = 5/71 (7%)	Presumed Eradicated = 61/71 (85.9%)
	Eradication +	Presumed Eradicated = 66/71 (93%)
		Presumed Persistence = 1/71 (1.4%)
		Recurrence = 4/71 (5.6%)
4. Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = 2		
	Patients Cured = 1/2 (50%)	Eradicated = 1/2 (50%)
	Patients Failures = 1/2 (50%)	Presumed Eradicated = 1/2 (50%)
	Eradication +	Presumed Eradicated = 2/2 (100%)
5. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 8		
	Patients Cured = 7/8 (87.5%)	Eradicated = 1/8 (12.5%)
	Patient Failures = 1/8 (12.5%)	Presumed Eradicated = 6/8 (75%)
	Eradication +	Presumed Eradicated = 7/8 (87.5%)
		Presumed Persistence = 1/8 (12.5%)

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

CAP Summary by Specific Pathogen

CAP Clinical Outcome and Bacteriological Outcome Results at TOC

TABLE 31* **CAP Protocols: #3012 & #4003 – Per Protocol (PP_b) Population**

Staphylococcus aureus

Continent	Clinical Outcome	Bacteriological Outcome

North America: 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%)

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

Europe: Number of patients isolated with *Staphylococcus aureus* at baseline = 5

Patients Cured = 4/5 (80%) Eradication = 1/5 (20%)
Patients Failed = 1/5 (20%) Presumed Eradicated = 3/5 (60%)
Eradication + Presumed Eradicated = 4/5 (80%)
Presumed Persistence = 1/5 (20%)

Africa: Number of patients isolated with *Staphylococcus aureus* at baseline = 7

Patients Cured = 7/7 (100%) Eradication = 1/7 (14.3%)
Presumed Eradicated = 6/7 (85.7%)
Eradication + Presumed Eradicated = 7/7 (100%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 30.

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.

TABLE 32* **New CAP Protocols: #3013 & #4003 – Per Protocol (PP_b) Population**

Streptococcus pneumoniae

Continent	Clinical Outcome	Bacteriological Outcome
North America: 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%)
South America: 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%)
Europe: Number of patients isolated with *Streptococcus pneumoniae* at baseline = 15		
	Patients Cured = 14/15 (93.3%)	Eradicated = 2/15 (13.3%)
	Patients Failures = 1/15 (6.7%)	Presumed Eradicated = 12/15 (80%)
		Eradication + Presumed Eradicated = 14/15 (93.3%)
		Presumed Persistence = 1/15 (6.7%)
Africa: Number of patients isolated with *Streptococcus pneumoniae* at baseline = 89		
	Patients Cured = 84/89 (94.4%)	Eradicated = 16/89 (18%)
	Patients Failures = 5/89 (5.6%)	Presumed Eradicated = 72/89 (80.9%)
		Eradication + Presumed Eradicated = 88/89 (98.9%)
		Presumed Persistence = 1/89 (1.1%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 30.

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%).

TABLE 33* **New CAP Protocols #3012 & #4003 – Per Protocol (PP_b) Population**

Haemophilus influenzae

Continent	Clinical Outcome	Bacteriological Outcome
North America: 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%)
South America: 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%)
Europe: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 9		
	Patients Cured = 7/9 (77.8%)	Eradicated = 1/9 (11.1%)
	Patients Failures = 2/9 (22.2%)	Presumed Eradicated = 6/9 (66.7%)
	Eradication +	Presumed Eradicated = 7/9 (77.8%)
		Presumed Persistence = 2/9 (22.2%)
Africa: Number of Patients isolated with *Haemophilus influenzae* at Baseline = 71		
	Patients Cured = 66/71 (93%)	Eradicated = 5/71 (7%)
	Patients Failures = 5/71 (7%)	Presumed Eradicated = 61/71 (85.9%)
	Eradication +	Presumed Eradicated = 66/71 (93%)
		Presumed Persistence = 1/71 (1.4%)
		Recurrence = 4/71 (5.6%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 30.

Combined Total Number of Patients isolated with *Haemophilus influenzae* at Baseline = 144

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.

TABLE 34* **New CAP Protocols #3012 & #4003 – Per Protocol (PP_b) Population**

Haemophilus parainfluenzae

Continent	Clinical Outcome	Bacteriological Outcome
North America:	Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = 35	
	Patients Cured = 31/35 (88.6%)	Presumed Eradicated = 27/35 (77.1%)
	Patient Failures = 4/35 (11.4%)	Persistence = 6/35 (17.1%)
		Presumed Persistence = 2/35 (05.7%)
South America:	Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = None.	
Europe:	Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = 3	
	Patients Cured = 3/3 (100%)	Presumed Eradicated = 3/3 (100%)
Africa:	Number of Patients isolated with *Haemophilus parainfluenzae* at Baseline = 2	
	Patients Cured = 1/2 (50%)	Eradicated = 1/2 (50%)
	Patients Failures = 1/2 (50%)	Presumed Eradicated = 1/2 (50%)
		Eradication + Presumed Eradicated = 2/2 (100%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 30.

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.

TABLE 35* **New CAP Protocols: #3012 & #4003 – Per Protocol (PP_b) Population**

Moraxella catarrhalis

Continent	Clinical Outcome	Bacteriological Outcome
North America: 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: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 1		
	Patients Cured = 1/1 (100%)	Recurrence = 1/1 (100%)
Europe: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 5		
	Patients Cured = 5/5 (100%)	Eradicated = 1/5 (20%)
		Presumed Eradicated = 4/5 (80%)
		Eradication + Presumed Eradicated = 5/5 (100%)
Africa: Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 8		
	Patients Cured = 7/8 (87.5%)	Eradicated = 1/8 (12.5%)
	Patient Failures = 1/8 (12.5%)	Presumed Eradicated = 6/8 (75%)
		Eradication + Presumed Eradicated = 7/8 (87.5%)
		Presumed Persistence = 1/8 (12.5%)

* Adapted from this Clinical Microbiologist's Review #3 found in Table 30.

Combined Total Number of Patients isolated with *Moraxella catarrhalis* 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.

New CAP Protocols: #3012 & #4003 – PP_b Summary Population Analyses

TABLE 36* Combined New CAP Clinical Outcome and Bacteriological Outcome Results at TOC

	Staphylococcus aureus	*Streptococcus pneumoniae*	*Haemophilus influenzae*	*Haemophilus parainfluenzae*	*Moraxella catarrhalis*
Patients with Isolates	25	144	124	40	20
Patients Cured	21/25 (84%)	135/144 (93.8%)	111/124 (89.5%)	35/40 (87.5%)	18/20 (90%)
Patient Failures	4/25 (16%)	9/144 (6.2%)	13/124 (10.5%)	5/40 (12.5%)	2/20 (10%)
Microorganisms Eradicated	3/25 (12%)	22/144 (15.2%)	6/124 (4.8%)	1/40 (2.5%)	2/20 (10%)
Microorganisms Presumed Eradicated	19/25 (76%)	17/144 (81.3%)	104/124 (83.9%)	31/40 (77.5%)	15/20 (75%)
Microorganisms (Eradicated + Presumed + Eradicated)	22/25 (88%)	139/144 (96.5%)	110/124 (88.7%)	32/40 (80%)	17/20 (85%)
Persistence	None	None	1/124 (0.8%)	6/40 (15%)	None
Presumed Persistence	3/25 (12%)	5/144 (3.5%)	9/124 (7.3%)	2/40 (5%)	2/20 (10%)
Recurrence	None	None	4/124 (3.2%)	None	1/20 (5%)

* Adapted from this Clinical Microbiologist's Review #3 found in Tables 31 to 35.

CAP Summary Conclusions on the new Protocols #3012 and #4003

In the new Community Acquired Pneumoniae (CAP) studies, Protocols #3012 and #4003, the combined clinical cure outcome rates and the bacteriological (eradication + presumed eradication) outcome rates for the PP_b population are summarized as described:

Note: PP_b = All PPc subjects with isolation of a causative pathogen from an adequate culture of pre-therapy or entry.

PP_c = All mITT subjects except those with major protocol violations and/or indeterminate responses.

- For *Staphylococcus aureus*, the patients cured and the bacteriological outcome (eradication and presumed eradication) are close: 21/21 (84%) and 22/25 (88%), respectively.
- For *Streptococcus pneumoniae* the patients cured and the bacteriological outcome (eradication and presumed eradication) are close: 135/144 (93.8%) and 139/144 (96.5%), respectively.
- For *Haemophilus* influenzae, the patients cured and the bacteriological outcome (eradication and presumed eradication) are close: 111/124 (89.5%) and 110/124 (88.7%), respectively.
- For *Moraxella catarrhalis*, the patients cured and the bacteriological outcome (eradication and presumed eradication) are close: 18/20 (90%) and 17/20 (85%), respectively.