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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-784**

Microbiology Review(s)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
Clinical Microbiological Review

NDA#: 50-784

REVIEW #: 1

COMPLETED DATE: 05/20/02

Reviewer: Harold V. Silver

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NAME & ADDRESS OF APPLICANT:

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SUBMISSION REVIEWED:

Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease (ABECB) in Adults, 3 days azithromycin dosing (500 mg/day), 1500 mg total, as an alternative to 5 Days dosing (500 mg on day 1, followed by 250 mg on days 2-5), also 1500 mg total. The Applicant is using a new blended 500 mg azithromycin film-coated tablet.

DRUG PRODUCT NAME:

Proprietary: ZITHROMAX® Tablets
Non-Proprietary/USAN: azithromycin (as azithromycin dihydrate)

DOSAGE FORM: Film-coated Tablet.

POTENCY: 500 mg azithromycin / tablet

ROUTE OF ADMINISTRATION: Oral

DISPENSED: x Rx OTC

RELATED DOCUMENT(s):

NDA 50-670, 250 mg Capsule, for the treatment of lower and upper respiratory infections, skin and skin structure infections, and sexually transmitted diseases, and Approved 11/01/91.
NDA 50-693, 1-g Single Dose Packet, Powder For Reconstitution, Approved 09/28/94.
NDA 50-710, 100 mg/5 mL and 200 mg/5 mL, Powder For Reconstitution, Approved 10/19/95.
NDA 50-711, 250 mg/Tablet, Approved 07/18/96.
NDA 50-730, 600 mg Tablet, Approved 07/12/96.

PHARMACOLOGICAL CATEGORY:

Macrolide antibiotic (azalide, a subclass of macrolide antibiotics)

FDA APPROVED INDICATIONS:

ADULTS:

- Acute Bacterial Exacerbations of Chronic Obstructive Pulmonary (AECB) disease due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.
- Community-Acquired Pneumonia (CAP) due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.
- Uncomplicated skin and skin structure infections (SSSI) due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

CHILDREN (pediatric):

- Acute Otitis Media (AOM) caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy
- Community-Acquired Pneumonia (CAP) due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

REMARKS/COMMENTS:

This is a review on NDA 50-784 that contains clinical and bacteriological data in support of "Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease" (ABECB) in Adults due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. The new accelerated azithromycin dose regimen is for 3 days dosing (500 mg/day), 1500 mg total, as an alternative to 5 Days dosing (500 mg on day 1, followed by 250 mg on days 2-5), also 1500 mg total. A new 500 mg azithromycin / film-coated tablet is being used.

CONCLUSIONS:

The DAIDP/HFD-520 Medical Officer concluded that the Applicant submitted "acceptable" clinical data to support the "approval" recommendation of ZITHROMAX (azithromycin as azithromycin dihydrate) Tablets for "Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease" (ABECB) in Adults due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

From the Clinical Microbiology Reviewer's perspective, the bacteriological data for NDA 50-784 on *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* are "acceptable" and the recommendation for NDA 50-784 is for "approval".

Package Insert Labeling – Microbiology and REFERENCES portions only:

The Clinical Microbiology Reviewer previously made current the **Microbiology** and **REFERENCES** portions of the labeling for "Zithromax (azithromycin) for Oral Suspension", supplemental NDA 50-710/SE2-008 and /SE2-009, respectively. The "approval" date was 12/14/01. This Package Insert labeling is being used for the labeling "template" for some of the other azithromycin drug products. Therefore, from the microbiological perspective the labeling is "approved" when the additional requested changes are made to the **Microbiology** and **REFERENCES** portions of the Package Insert for NDA 50-784. The requested informational statement addition can be found under the "Clinical Microbiologist's Comment" on page 85. The final recommended version of the **Microbiology** and **REFERENCES** portions of the Package Insert can be found on pages 60 to 63 in this review.

A summary of the bacteriological eradication results in Protocol A0661013 is described as follows:

-- Modified-to-Treat (MITT) Population:

The bacteriological (i.e., eradication + presumed eradication) rates for the Applicant's targeted microorganisms in the Modified-to-Treat (MITT) population are as follows: *Haemophilus influenzae* 10/15 (66.7%), *Moraxella catarrhalis* 10/12 (83.3%), and *Streptococcus pneumoniae* 30/33 (90.9%), respectively. Although the combined *Haemophilus influenzae* number of isolates (10/15) and corresponding bacteriological outcome rate (66.7%) are both low, the results are within the expected percentage range.

-- Per Protocol (PP) Population:

The bacteriological (i.e., eradication + presumed eradication) rates for the Applicant's targeted microorganisms in the Per Protocol (PP) population are as follows: *Haemophilus influenzae* 10/16 (62.5%), *Moraxella catarrhalis* 11/13 (84.6%), and *Streptococcus pneumoniae* 27/31 (87.1%), respectively. Again, although the *Haemophilus influenzae* number of isolates (10/16) and corresponding bacteriological outcome rate (62.5%) are low, the bacteriological outcome rate of azithromycin versus *Haemophilus influenzae* is within the expected percentage range.

-- Comparison of the Modified-to-Treat (MITT) and Per Protocol (PP) Populations:

The bacteriological eradication (i.e., eradication + presumed eradication) outcome rates for the Applicant's targeted microorganisms (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) for the Modified-to-Treat (MITT) and the Per Protocol (PP) populations are very close and are "acceptable". Although the *Haemophilus influenzae* number of isolates and corresponding bacteriological eradication outcome rates for the MITT, 10/15 (66.7%), and the PP, 10/16 (62.5%), populations are both low, the bacteriological eradication outcome rates are within the expected percentage range.

EXECUTIVE SUMMARY

NDA 50-784

Pfizer, Inc.

ZITHROMAX® (as azithromycin dihydrate) 500 mg Film-Coated Tablet

Introduction

The Applicant submitted NDA 50-784 which contains clinical and bacteriological data in support of their claim for "Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease" (ABECB) in Adults due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. The new accelerated azithromycin dose regimen is for 3 days dosing (500 mg/day), 1500 mg total, as an alternative to 5 Days dosing (500 mg on day 1, followed by 250 mg on days 2-5), also 1500 mg total.

The Applicant used a new film-coated blended 500 mg tablet. The tablet is a scaled-up version of the commercial 250 mg tablet. They cross-referenced to their NDA 50-711, 250 mg/ Tablet, approved on 07/18/96. Both tablets are made from a common tablet blend, are coated with the same coating materials, and differ only in size and weight. The applicant submitted data of comparative dissolution studies between the 2 tablet strengths as an alternative to conducting *in vivo* bioequivalence studies. Dr. Charles Bonapace, Bio-Pharm Reviewer and Dr. Andy Yu, Chemistry Reviewer, concurred that the submitted data are "acceptable".

Mechanism of Action

Azithromycin acts by binding reversibly to the 23S component of the 50S ribosomal subunit of susceptible microorganisms, blocking the translocation reaction of polypeptide chain elongation, and thereby interferes with microbial protein synthesis. Nucleic acid synthesis is not affected.

Antimicrobial Spectrum of Activity

The "Alexander Project" [1] was established in 1992 to monitor the susceptibility of the major lower respiratory tract bacterial pathogens to a variety of antimicrobials and to identify trends on the development of resistance over time. Results from the Alexander project, 1996-1997, showed that 21.9% of *Streptococcus pneumoniae* isolates collected from community-acquired lower respiratory tract infections in multiple countries were resistant to macrolides. In the USA, 16.9% and 21.9% of *Streptococcus pneumoniae* strains were resistant to azithromycin overall in 1996 and 1997, respectively, while 56.5% of penicillin-resistant strains were azithromycin-resistant. Results from the recent Alexander Project showed that 99.9% and 100% of the *Haemophilus influenzae* and *Moraxella catarrhalis* isolates, respectively, were susceptible to azithromycin throughout Europe.

The "SENTRY Antimicrobial Surveillance Program" [2] studied the *in vitro* activities of numerous antimicrobials against clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with bloodstream and respiratory tract infections in the United States (26 to 28 laboratory sites), Canada, Europe, Latin America and the Asia-Pacific region. Surveillance studies with recent United States isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* showed virtually all the isolates (>99%) were susceptible to azithromycin [2, 3, 4]. A 1997-1998 surveillance study [5] involving 34 medical centers in the United States and a total of 1,601 *Streptococcus pneumoniae* strains found that 1,295/1,601 (80.9%) of isolates from patients were susceptible to azithromycin and 299/1601 (18.7%) isolates from patients were resistant.

Bactericidal Activity

The use of azithromycin to treat respiratory tract infections has two advantages over using cell wall-active antibiotics that cause lysis of cells. Although azithromycin is bactericidal to many *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* strains [6], the cells largely remain intact. However, the action of a β -lactam antibiotic often results in cellular lysis, releasing pro-inflammatory components of the cell surface (like peptidoglycan or lipoteichoic acids from Gram-positive bacteria or lipopolysaccharide from Gram-negative bacteria) that have been shown to exacerbate the inflammatory response [7]. In addition to downstream-damaging effects that occur as a result of the cellular debris, DNA is released. The use of a protein synthesis inhibitor like azithromycin has a dual advantage: 1) DNA exchange (including shuffling of resistance determinants) via transformation is not promoted and 2) the cascade of inflammatory events triggered by cell wall components is significantly reduced because cells remain intact. Additionally, azithromycin, by inhibiting protein synthesis even at sub-MIC concentrations, may prevent the production of toxins or other virulence factors. The reported intrinsic anti-inflammatory properties of azithromycin may also contribute to dampening the destructive immune response triggered by pro-inflammatory cellular components [8, 9, 10].

Mechanisms of Resistance

There are 2 widespread mechanisms of macrolide resistance in *Streptococcus pneumoniae* – *erm(B)* and *mef(A)*. *Erm(B)* encodes a ribosomal methylase that adds 2 methyl groups to A2058 in 23S rRNA, thereby reducing the binding affinity for macrolides and two other structurally unrelated antibiotic classes, lincosamides and streptogramin B. *Mef(A)* encodes an efflux pump specific for 14- and 15-membered macrolides.

Although the majority of macrolide-resistant pneumococcal strains can be accounted for by containing either *mef(A)* or *erm(B)*, there have been recent reports of clinical isolates that have either mutations in three of the four 23S rRNA alleles at position 2059 or a mutation in a highly conserved region of ribosomal protein L4 [11, 12].

Efflux can be mediated by either a pump with narrow specificity (e.g., *Mef(A)*, *Msr(A)*) or a pump with broad specificity (e.g., *AcrAB-TolC*, *MexAB-OprM*, *AmrAB-OprA*, *MtrCDE*, *MdfA*, *Cmr*) [13, 14, 15]. Many of the pumps with broad specificity are intrinsic to the species. The *AcrAB-TolC* pump or at least one homologue of this tripartite pump found exclusively in Gram-negative bacteria like *Escherichia coli* and *Haemophilus influenzae* are responsible for the innate resistance of Gram-negative species to macrolides and other hydrophobic compounds.

Summary of the Bacteriological Results

– Modified-to-Treat (MITT) Population:

The bacteriological (i.e., eradication + presumed eradication) rates for the Applicant's targeted

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ZITHROMAX® (azithromycin) 500 mg Film-Coated Tablet

microorganisms in the Modified-to-Treat (MITT) population are as follows: *Haemophilus influenzae* 10/15 (66.7%), *Moraxella catarrhalis* 10/12 (83.3%), and *Streptococcus pneumoniae* 30/33 (90.9%), respectively. Although the combined *Haemophilus influenzae* number of isolates (10/15) and corresponding bacteriological outcome rate (66.7%) are both low, the results are within the expected percentage range.

-- Per Protocol (PP) Population:

The bacteriological (i.e., eradication + presumed eradication) rates for the Applicant's targeted microorganisms in the Per Protocol (PP) population are as follows: *Haemophilus influenzae* 10/16 (62.5%), *Moraxella catarrhalis* 11/13 (84.6%), and *Streptococcus pneumoniae* 27/31 (87.1%), respectively. Again, although the *Haemophilus influenzae* number of isolates (10/16) and corresponding bacteriological outcome rate (62.5%) are low, the bacteriological outcome rate of azithromycin versus *Haemophilus influenzae* is within the expected percentage range.

-- Comparison of the Modified-to-Treat (MITT) and Per Protocol (PP) Populations:

The bacteriological eradication (i.e., eradication + presumed eradication) outcome rates for the Applicant's targeted microorganisms (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) for the Modified-to-Treat (MITT) and the Per Protocol (PP) populations are very close and are "acceptable". Although the *Haemophilus influenzae* number of isolates and corresponding bacteriological eradication outcome rates for the MITT, 10/15 (66.7%), and the PP, 10/16 (62.5%), populations are both low, the bacteriological eradication outcome rates are within the expected percentage range.

Conclusion

From the Clinical Microbiology Reviewer's perspective, the bacteriological data for NDA 50-784 on *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* are "acceptable" and the recommendation for NDA 50-784 is for "approval".

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I. INTRODUCTION

The Applicant submitted NDA 50-784 that contains clinical and bacteriological data in support of their proposed indication "Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease" (ABECB) in Adults due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. This is a new accelerated azithromycin dose regimen for 3 days dosing (500 mg/day), 500 mg total, as an alternative to 5 days dosing (500 mg on day 1, followed by 250 mg on days 2-5), also 1500 mg total. A new 500 mg azithromycin / film-coated tablet is being used.

The **MICROBIOLOGY** and **REFERENCES** portions of the Package Labeling for NDA 50-784 follows the previously "approved" (12/14/01) labeling for NDA 50-710. However, some additional revisions were made.

II. PRECLINICAL EFFICACY (*IN VITRO*)

Azithromycin is an approved drug. Much of the information can be found in the original NDA 50-670, "approved" 11/01/91, subsequent "approved" **RELATED DOCUMENT(s)** found on page 1 of this Review, including the recent efficacy supplement NDA 50-710/SE2-008 and -/SE2-009, "approved" on 12/14/01.

A. Mechanism of Action

Azithromycin acts by binding reversibly to the 23S component of the 50S ribosomal subunit of susceptible microorganisms, blocking the translocation reaction of polypeptide chain elongation, and thereby interferes with microbial protein synthesis. Nucleic acid synthesis is not affected.

B. Antimicrobial Spectrum of Activity

Much of the information on the *in vitro* spectrum and potency of azithromycin is identical to that submitted with the original submission, NDA 50-670, subsequent "approved" **RELATED DOCUMENT(s)** found on page 1 and of this Review, including the recent efficacy supplement NDA 50-710/SE2-008 and /SE2-009, "approved" on 12/14/01. Some of the most recent published data on susceptibility and resistance to the targeted pathogens are discussed below.

The "Alexander Project" [1] was established in 1992 to monitor the susceptibility of the major lower respiratory tract bacterial pathogens to a variety of antimicrobials and to identify trends on the development of resistance over time. Results from the Alexander project, 1996-1997, showed that 21.9% of *Streptococcus pneumoniae* isolates collected from community-acquired lower respiratory tract infections in multiple countries were resistant to macrolides. In the USA, 16.9% and 21.9% of *Streptococcus pneumoniae* strains were resistant to azithromycin overall in 1996 and 1997, respectively, while 56.5% of penicillin-resistant strains were azithromycin-resistant. Results from the recent Alexander Project also showed that 99.9% and 100% of the *Haemophilus influenzae* and *Moraxella catarrhalis* isolates, respectively, were susceptible to azithromycin throughout Europe.

The "SENTRY Antimicrobial Surveillance Program" [2] studied the *in vitro* activities of numerous antimicrobials against clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with bloodstream and respiratory tract infections in the United States (26 to 28 laboratory sites), Canada, Europe, Latin America and the Asia-Pacific region. This study of respiratory tract and blood stream isolates collected in 1997-1999 from countries in the Western Hemisphere, Europe, and Asia-Pacific, azithromycin resistance ranged from 8.1% in Canada to 36.7% in Asia-Pacific. Resistance to azithromycin in the United States in this study was 13.6%. The SENTRY report of respiratory isolates from 1997-1999 lists azithromycin resistance at 8.1% worldwide. It appeared that the majority of macrolide-resistant pneumococci in the United States harbor *mef(A)*, a gene that encodes an efflux pump for 14- and 15-membered macrolides. In the Atlanta metropolitan area, the incidence of *mef(A)*-mediated macrolide resistance in

invasive pneumococci changed significantly over the six years of study (1994-1999). The SENTRY Antimicrobial Surveillance Program found the rate of resistance to another macrolide, clindamycin, largely unchanged during 1997-1999, commensurate with an increase in resistance due to isolates harboring the efflux gene. Surveillance studies with recent United States isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* showed virtually all the isolates (>99%) were susceptible to azithromycin [2,3,4]. In one of the studies the *in vitro* activity of 24 antimicrobial agents against 6,242 respiratory tract isolates of *Haemophilus influenzae* collected in the SENTRY program (1997-1999) in the Western Hemisphere, Europe, and the Asia-Pacific region demonstrated that the azithromycin MIC₉₀ for *H. influenzae* is generally 2 µg/ml as compared with 16 µg/ml for clarithromycin.

Investigators [5] analyzed 4,489 pneumococci isolated from 92 centers in the USA between June 1996-April 1997. The investigators found 12-16.4% macrolide resistance.

A 1997-1998 surveillance study [6] involving 34 medical centers in the United States and a total of 1,601 *Streptococcus pneumoniae* strains found that 1,295/1,601 (80.9%) of isolates from patients were susceptible to azithromycin and 299/1601 (18.7%) isolates from patients were resistant.

Another large USA study [7] involving 51 medical centers and 2,752 isolates from outpatient clinics during 1996-97, report 22.8% and 22.7 % of *S. pneumoniae* resistant to azithromycin and clarithromycin, respectively. An associated US study, "Survey of Susceptibilities of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* Isolates to 23 Antimicrobial Agents: a Prospective U.S. Study", reports 99.7% of 1,032 *H. influenzae* strains susceptible to azithromycin (MIC₉₀ = 2 µg/ml).

A recent publication [8] of US isolates documented increasing resistance to macrolides, 11% to 15% from 1995 to 1998, respectively, for invasive pneumococcal isolates.

Macrolide resistance in Canada is approximately half (9.3%) of what is seen in the US, according to a recent surveillance report [9] of 1,180 respiratory isolates of *S. pneumoniae* (1997-1998).

Another recent surveillance study [10] of 1,531 isolates of pneumococci from 33 medical centers in the US revealed an azithromycin MIC₉₀ of 16 µg/ml, confirming that the major mechanism of resistance is an efflux pump encoded by *mef(A)*.

A 1999 study [11, 12] analyzed the prevalence of penicillin resistance among 698 *Streptococcus pneumoniae* isolates from 20 European University Hospitals participating in the "European SENTRY Antimicrobial Surveillance Programme". Antimicrobial susceptibility testing of isolates was performed using reference broth microdilution methods according to the National Committee for Clinical Laboratory Standards (NCCLS) recommended guidelines. Quality control was performed using *Streptococcus pneumoniae* ATCC 49619. NCCLS defined breakpoints were used to interpret MIC data. This surveillance study demonstrated levels of resistance to azithromycin ranged from (33/507) 6.6% for penicillin-susceptible strains to 22/43 (51.2%) for penicillin-resistant strains. Although no genotyping was done to confirm that macrolide-resistant, clindamycin-susceptible isolates contained *mef(A)*, the latter appeared to constitute 2.3%, 4.1%, and 6.2% of the penicillin-susceptible (PenS), intermediately penicillin-resistant (PenI), and high-level penicillin-resistant (PenR) strains, respectively. The majority of macrolide-resistant isolates appeared to harbor resistance mediated by *erm*, a 23S rRNA methyltransferase.

Some other studies [4, 13, 14] demonstrated that pneumococci from the United States appeared to harbor *mef(A)* more often than *erm* genes, isolates from countries like France, Italy, Austria, Spain, Greece, and Belgium are 2-3 times more likely to carry *erm(B)* [15].

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TABLE 1** lists the surveillance figures for penicillin and macrolide resistance in *Streptococcus pneumoniae* isolates from different parts of Europe and the United States.

TABLE 1**

<u>Country</u>	<u>Year</u>	<u>Total No. Isolates</u>	<u>% PenI</u>	<u>% PenR</u>	<u>% MacR</u>	<u>Reference</u>
Austria	1996	217		0.9		(2)
			6.5		4.6	
Belgium	1996	287	3.5	10.1	22	(2)
	1997	264	4.5	5.7	31.1	(2)
	1997-1998	38	18	0	15.8	(14)
	1998	1205	11.2	3.0	31.0	(23)

NDA 50-784
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Canada	1997	54	22.2	11.1	5.6	(24)
	1997-1999	887		6.8	8.1	(4)
Czech Republic	1996	78	0	0	0	(2)
	1997	93	2.2	3.2	2.2	(2)
Europe	1997-1999	1478		10.4	17.8	(4)
France	1996	165	10.3	32.1	40.6	(2)
	1997	181	20.4	29.3	45.9	(2)
	1997	2837	19	25	53.1	(25)
	1997-1998	221		66.5	58.4	(3)
Germany	1997-1998	145	32.4	11.7	33.1	(14)
	1996	75	4	0	2.7	(2)
	1997	62	14.5	0	6.5	(2)
	1997-1998	283		7.8	9.9	(3)
	1997-1998	122	18.0	1.6	10.7	(14)
Hungary	1996	127	24.4	11.8	13.4	(2)
Ireland	1997	87	10.3	13.8	13.8	(2)
Italy	1996	237	4.2	4.9	24.1	(2)
	1997	191	4.2	3.1	29.8	(2)
	1998	900		12.7 ^a	31.7	(26)
	1999	913		10.2 ^a	25.5	(26)
	1997-1998	370		16.8 ^a	24.3	(3)
	1997-1998	32	25	0	31.2	(14)
Latin America	1997-1999	948		11.7 ^a	8.6	(4)
Mexico	1996	51	31.4	15.7	31.4	(2)
	1997	63	12.7	36.5	15.9	(2)
Netherlands	1996	65	1.5	3.1	1.5	(2)
North America	1997-1998	1665	15	12.2	36 [*]	(27)
Poland	1997-1998	60	26	4	11.6	(14)
Portugal	1999	312	13.5	11.2	13.8	(28)
Spain	1996	136	18.4	22.8	19.1	(2)
	1997	175	16.6	34.8	32.6	(2)
	1990-1999	2661	45.7	12.7	34.2	(29)
	1997-1998	125	33.6	8.0	10.4	(14)
	1997-1998	320		65.6 ^a	37.8	(3)

TABLE 1^{} (con't)**

<u>Country</u>	<u>Year</u>	<u>Total No. Isolates</u>	<u>% PenI</u>	<u>% PenR</u>	<u>% MacR</u>	<u>Reference</u>
Switzerland	1996	94	7.4	3.2	6.4	(2)
	1997	158	5.7	4.4	15.8	(2)
	1997-1998	72	11	1	14.6	(14)
Turkey	1994	70	30	17	10	(30)
	1996-1999	750	29	3	8	(31)
UK	1996	88	4.5	4.5	13.6	(2)
	1997	111	6.3	6.3	7.2	(2)
	1997-1998	343		10.8 ^a	8.7	(2)

USA	1996	79	12.7	16.4	13.9	(2)
	1996-1997	4489	23.6	12.9	12.7	(5)
	1997	159	34.6	7.5	5.7*	(24)
	1997	124	15.3	18.6	16.9	(2)
	1998	195		23.2 ^a	11.6	(32)
	1998	Not given		25.0 ^a	15.0	(8)
	1998	4013		25 ^a	15*	(8)
	1997-1998	1665	15.0	12.2	16.9	(27)
	1997-1998	1601	17.4	12.1	18.7	(6)
	1997-1999	4193		14.0 ^a	13.6	(4)
	1999-2000	1531	12.7	21.5	26.2	(10)

^a Adopted from NDA 50-784, Dated 07/27/01, Vol. 23, "Antimicrobial Spectrum of Activity", pages 6 & 7.

Susceptibility categories are those defined by NCCLS:

PenI = intermediate resistance to penicillin;

PenR = high-level penicillin resistance;

MacR = macrolide resistance as represented by azithromycin unless indicated with (*)
 where * = erythromycin; and

^a = penicillin resistance was reported as a combination of intermediate and high-level penicillin resistance.

Note: The REFERENCES listed in the aforementioned table can be found in NDA 50-784, Dated 07/27/01, Vol. 23, pages 53 to 66.

Clinical Microbiologist's Comments:

As seen, in TABLE 1, in most of the European and other non-US countries, penicillin-resistant *Streptococcus pneumoniae* (PRSP) and macrolide-resistant *Streptococcus pneumoniae* (MacRSP) have also increased in the United States over the years.

C. Bactericidal Activity

The use of azithromycin to treat respiratory tract infections may have two advantages over using cell wall-active antibiotics that cause lysis of cells. Although azithromycin is bactericidal to many *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* strains [16], the cells largely remain intact. However, the action of a β -lactam antibiotic often results in cellular lysis, releasing pro-inflammatory components of the cell surface (like peptidoglycan or lipoteichoic acids from Gram-positive bacteria or lipopolysaccharide from Gram-negative bacteria) that have been shown to exacerbate the inflammatory response [17]. In addition to downstream-damaging effects that occur as a result of the cellular debris, DNA is released. The use of a protein synthesis inhibitor like azithromycin has a dual advantage: 1) DNA exchange (including shuffling of resistance determinants) via transformation is not promoted and 2) the cascade of inflammatory events triggered by cell wall components is significantly reduced because cells remain intact. Additionally, azithromycin, by inhibiting protein synthesis even at sub-MIC concentrations, may prevent the production of toxins or other virulence factors. The reported intrinsic anti-inflammatory properties of azithromycin may also contribute to dampening the

destructive immune response triggered by pro-inflammatory cellular components [18, 19, 20].

D. MISCELLANEOUS STUDIES

pH

The original submission on oral azithromycin, NDA 50-670, contained experimental data demonstrating how the *in vitro* potency of macrolides and especially azithromycin is affected by the pH of the growth media. Recent studies have extended and confirmed previous results showing that incubation of microtiter or agar plates in a CO₂ environment lowers the pH of the growth medium and results in overestimation of resistance in streptococci and *Haemophilus* [21, 22]. This is true when the E-test procedure is used as incubation in CO₂ [22, 23]. Currently, the E-test is not acceptable for testing of macrolides under NCCLS guidelines [24]. Another study has documented the increased potency of azithromycin against a broad spectrum of anaerobic species when the pH of the medium is controlled [25].

E. Post-Antibiotic and Post-Antibiotic Sub-MIC Effects

1. Postantibiotic Effect (PAE):

Reports of PAEs of between 2.2 and 4.7 h have been observed for *Streptococcus pneumoniae* [26, 27] and *Haemophilus influenzae* [26, 27, 28,]. A very long post-antibiotic sub-MIC effect (SME) (14.4 h) of azithromycin has been noted for *H. influenzae* at 0.3X MIC [27]. A recent paper reported a PAE of >12 h for a penicillin-resistant isolate of *S. pneumoniae* and a mean PAE of 2 h for *Moraxella catarrhalis* strains [29]. The PAE of 5X the MIC of azithromycin against 20 pneumococci ranged from 1 to 6h [30]. In the latter study, the PAE of the sub-MIC concentrations of 0.125, 0.25, and 0.5 times the MIC ranged from 1 to 8, 1 to 8, and 1 to 6 h, respectively. *In vivo* azithromycin PAEs of 11 h for *S. pneumoniae* have been reported using the neutropenic mouse thigh model [26]. A significant decrease in the virulence of post-antibiotic-phase pneumococci was measurable by increases in LD₅₀ values (31). The SME of azithromycin at 0.1X, 0.2X, or 0.3X the MIC for *S. pneumoniae* was 1.7, 6.2, or 12.0 h, respectively. The *in vivo* postantibiotic effects seen with azithromycin are partly a function of its long half-life and account for significant suppression of growth for extended periods even at sub-MIC concentrations [26, 31].

2. Post-Antibiotic Sub-MIC:

In vitro laboratory experiments do not suggest that resistance emerges rapidly to azithromycin, even when the organisms are grown in the presence of sub-MIC concentrations of azithromycin [15, 32-37]. However, resistant *Streptococcus pneumoniae* strains have been shown to emerge after long-term passage (generally between 25-50 passages) in sub-inhibitory concentrations of macrolides [15, 32-37]. In studies where resistance development was monitored for five susceptible pneumococcal strains, more passages with azithromycin (average number = 28 subcultures) versus clarithromycin (15 subcultures) or erythromycin (23 subcultures) were required to see mutations [37]. The resistance that develops in *S. pneumoniae* strains after passage results from a mutation in 23S rRNA, specifically in nucleotides 2057-2059 or 2611 in domain V, or as a consequence of mutations in ribosomal proteins L4 or L22 [32-34, 36].

F. Mechanisms of Resistance Studies

There are 2 widespread mechanisms [NDA 50-710/SE2-008 and -/SE2-009, approved 12/14/02] of macrolide resistance in *Streptococcus pneumoniae* – erm(B) and mef(A). Erm(B) encodes a

ribosomal methylase that adds 2 methyl groups to A2058 in 23S rRNA, thereby reducing the binding affinity for macrolides and two other structurally unrelated antibiotic classes, lincosamides and streptogramin B. Mef(A) encodes an efflux pump specific for 14- and 15-membered macrolides.

Although the majority of macrolide-resistant pneumococcal strains can be accounted for by containing either *mef(A)* or *erm(B)*, there have been recent reports of clinical isolates that have either mutations in three of the four 23S rRNA alleles at position 2059 or a mutation in a highly conserved region of ribosomal protein L4 [15, 38].

Efflux can be mediated by either a pump with narrow specificity (e.g., Mef(A), Msr(A)) or a pump with broad specificity (e.g., AcrAB-TolC, MexAB-OprM, AmrAB-OprA, MtrCDE, MdfA, Cmr) [39, 40, 41]. Many of the pumps with broad specificity are intrinsic to the species. The AcrAB-TolC pump or at least one homologue of this tripartite pump found exclusively in Gram-negative bacteria like *Escherichia coli* and *Haemophilus influenzae* are responsible for the innate resistance of Gram-negative species to macrolides and other hydrophobic compounds.

There are only three isolates (all from the United States) known with the A2059G mutations as the sole resistance mechanism. Only one strain with a mutation in ribosomal protein L4 has been described in North America (a Canadian isolate) [38]; the remainder of strains with L4 mutations originate from Eastern European countries, where in one study they accounted for >20% of resistant strains [15]. A second type of *erm* gene, *erm(A)* (subclass *erm(TR)*) has also been described in clinical isolates of *S. pneumoniae* in Greece and Spain [42-43].

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III. PRECLINICAL EFFICACY (IN VIVO)

Pharmacokinetics and Pharmacodynamics

Using the *Streptococcus pneumoniae* neutropenic mouse thigh model, it has been found that efficacy for azithromycin correlated best with the ratio of the area under the serum concentration versus time curve (AUC) over the microorganism's MIC (24 h AUC/MIC ratio) [26, 44]. In contrast, efficacy with erythromycin and clarithromycin correlates best with the time that serum levels exceed the MIC.

1. Animal Model Studies

The original powder for oral suspension, NDA 50-670, described several acute, closed-space, localized and intracellular infection model studies in which good efficacy for azithromycin as compared to other commercial antibiotics was demonstrated. For the localized and intracellular infections, this efficacy correlated with the sustained high tissue levels of azithromycin.

A hypothesis to explain the transfer of azithromycin from tissue cells to non-intracellular pathogens growing in contact with the tissue cells has been proposed [45].

Recently, the results from a mouse model demonstrated azithromycin administered as a single dose significantly increased survival versus a pneumococcal challenge compared with all the other dose regimens [46]. These data suggest that the high initial concentrations of azithromycin favor a good outcome.

2. Human Studies:

The Applicant's Study #066-087 was a comparative, two-way cross-over design protocol in 12 healthy adult subjects designed to measure concentrations of azithromycin in serum and leukocytes following a 3-day azithromycin regimen (500 mg/day for 3 days) and a 5-day azithromycin regimen (500 mg on day 1 and 250 mg on days 2-5). Mean serum concentrations of azithromycin for both regimens were similar on day 1, but greater on days 2 and 3 of the 3-day regimen than on days 2 and 3 of the 5-day regimen. The mean values of AUC_{0-∞} obtained from the modeled data were 15.2 mg×hr/ml following the 3-day regimen and 14.5 mg×hr/ml following the 5-day regimen. The ratio of AUC_{0-∞} (3-day)/AUC_{0-∞} (5-day) was 105% with 90% confidence limits (CL) of 93% and 120% (p=0.49). The mean value of T_{1/2} was 68.6 hr following the 3-day regimen and 66.0 hr. following the 5-day regimen.

White blood cell pharmacokinetics were also examined with final measurements made at 288 hours after the first dose. The comparable AUC_{0-∞} values of the serum concentration-time curves and comparable AUC₀₋₂₈₈ values of the MNL and PMNL concentration-time curves demonstrate that comparable azithromycin exposure is achieved when the same total dose, 1.5 gm of azithromycin, is administered using either the 3-day or 5-day dosing regimens.

After oral dosing of azithromycin, serum concentrations do not appear sufficient to account for the good efficacy observed. As described in the original application and supplemental NDA 50-720/SE2-008 and /SE2-009, efficacy appears to be related to the sustained high levels of azithromycin in tissues and white blood cells. The delivery and maintenance of high concentrations of azithromycin at the site of infection have been shown to be mediated by the phagocyte delivery mechanism [46-54]. In the case of a bacteremic *Streptococcus pneumoniae* infection, the high tissue levels as well as macrophage-mediated delivery of azithromycin at the site of infection, would eliminate the focus of the infection in the lung, thereby preventing further spread of *S. pneumoniae* into the circulation [45]. Any remaining *S. pneumoniae* circulating in the bloodstream would be filtered and killed in the spleen or by white blood cells or other tissues with high concentrations of azithromycin.

Azithromycin, given as a single 500 mg dose to patients undergoing fiberoptic bronchoscopy, concentrated highly in alveolar macrophages (23 mg/ml), bronchial mucosa (3.89 mg/ml), epithelial lining fluid (2.18 mg/ml), and sputum (1.56 mg/ml), with maximum concentrations occurring 48 hours after dosing [55]). In another study a single oral dose of 500 mg azithromycin was given to patients 24, 72, 96, or 120 hours prior to elective pulmonary surgery [56]. Although the plasma levels were barely detectable 24 hours post-dose, high and sustained drug levels were found in lung tissue. Azithromycin levels were 3.10 mg/g (SD ± 2.17), 2.55 mg/g (SD ± 1.36), 3.94 mg/g (SD ± 2.40), and 3.13 mg/g (SD ± 0.50) in lung tissue at 24, 72, 96, and 120 hours post-dosing. These studies are consistent with the notion that a short-course of azithromycin therapy could be efficacious to treat susceptible respiratory pathogens since the MIC₉₀ values for *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are ≤ 0.5 µg/ml, 1-2 µg/ml, and ≤ 0.5 µg/ml, respectively. Published clinical studies [57-60] have confirmed that a shorter course of azithromycin therapy is as efficacious as longer, multiple daily dose treatments with other oral antimicrobial agents.

Several studies have assessed the azithromycin concentrations in lung tissues and pulmonary macrophages. After a single 500 mg oral dose was administered to 22 adult subjects undergoing bronchoscopy, azithromycin concentrations were measured at various intrapulmonary sites. Mean peak alveolar macrophage (AM) concentrations were six-fold greater than bronchial mucosal concentrations. Bronchial mucosal concentrations were significantly greater than epithelial lining fluid (ELF) concentrations; and these, in turn, were greater than sputum concentrations. The mean serum concentration was low [55]. This was further confirmed comparing the steady state concentrations of clarithromycin and azithromycin in plasma, ELF, and AM obtained by bronchoscopy from 40 healthy nonsmoking adult volunteers [61].

IV. BIOEQUIVALENCE

The Applicant used a new film-coated blended 500 mg tablet. The tablet is a scaled-up version of the commercial 250 mg tablet. They cross-referenced to their NDA 50-711, 250 mg/Tablet, approved 07/18/96.

Both tablets are made from a common tablet blend, are coated with the same coating materials, and differ only in size and weight.

The Applicant submitted data of comparative dissolution studies between the 2 tablet strengths as an alternative to conducting *in vivo* bioequivalence studies.

This Clinical Microbiology Reviewer spoke to Dr. Charles Bonapace, Bio-Pharm Reviewer. Dr. Bonapace mentioned that he and Dr. Andy Yu, Chemistry Reviewer, concurred that the submitted results were "acceptable".

V. CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

A. Clinical Laboratory Susceptibility Test Methods

Susceptibility Breakpoints:

Susceptibility tests were carried out, according to NCCLS susceptibility procedures, for all baseline respiratory pathogens isolated from sputum culture, with respect to azithromycin (and clarithromycin). NCCLS interpretative criteria were used for both MICs and zone size interpretation.

TABLE 2 shows the Applicant's MIC ($\mu\text{g/mL}$) and zone diameter (mm) susceptibility breakpoints used for the azithromycin studies.

Pathogen	Susceptible		Intermediate		Resistant	
	MIC ^a	Zone Diameter ^b	MIC ^a	Zone Diameter ^b	MIC ^a	Zone Diameter ^b

<i>Streptococcus</i> spp. including <i>Streptococcus pneumoniae</i>	≤0.5	≥18	1	14-17	≥2	≤13
<i>Haemophilus Influenzae</i>	≤4	≥12	—	^c	^c	^c
<i>Moraxella Catarrhalis</i>	≤2	≥18	4	14-17	≥8	≤13

^a Adopted from NDA 50-784, Vol. 23, on Page 22.

^a MIC (μ/mL); ^b Zone diameter (mm); ^c Current absence of data on resistant strains precludes defining any resistant categories other than "susceptible" for azithromycin.

Clinical Microbiology Comment:

The Applicant should have actually referred to the FDA "approved" susceptibility breakpoints for both MICs and zone size interpretation for azithromycin (clarithromycin). Sometimes, the FDA and NCCLS susceptibility breakpoints may differ. However, in this case, both the FDA and NCCLS microbial susceptibility breakpoints, as well as the microbial Quality Control (QC) ranges are the same.

B. Quality Control (QC)

For the Clinical Protocol A0661013, QC strains *Haemophilus influenzae* ATCC 49247 and *Streptococcus pneumoniae* ATCC 49619 were used in the quality control testing for both disk diffusion as well as the Microdilution Broth Method (MIC) tests. QC testing was performed with each batch of susceptibility tests.

The Quality Control tests were performed in accordance to:

1. NCCLS guideline M2-A7 and interpretation was made according to Table 3A, "Acceptable zone diameter Quality Control limits for Fastidious Organisms"; and
2. NCCLS guideline M7-A5, and interpretation was made according to Table 3A, "Acceptable Quality Control Limits of Minimal Inhibitory Concentrations (MICs) for Fastidious Organisms".

For all susceptibility data reported by the central laboratory, results of QC strain testing fell within NCCLS-specified limits.

Pathogen Identification:

The central laboratory also conducted susceptibility testing on all respiratory pathogens using azithromycin and clarithromycin. Isolation of a baseline pathogen susceptible to azithromycin or

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clarithromycin was not required to continue in the study.

Susceptibility testing was performed only for isolates confirmed by the central laboratory to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, or *Haemophilus parainfluenzae*.

Freshly expectorated sputum samples were examined macroscopically and microscopically to determine suitability for culture. Adequate specimens were submitted for culture with Gram stains to an approved local laboratory. The Gram stains and any culture isolates from the local laboratories were sent to the central laboratory, _____ to verify adequacy of Gram stain and to confirm the identification of the bacteria.

Spirometry equipment, _____ was supplied, and individual pulmonary function tests were analyzed by a central laboratory, _____. The urinary antigen test kits (NOW® *Streptococcus pneumoniae* urinary antigen test) were supplied by Binax, Inc., Portland, ME, and U.S.

Urine Antigen:

A correlation of *Streptococcus pneumoniae* urine antigen with sputum culture results was performed in order to assess the utility of this test for predicting clinical disease due to *Streptococcus pneumoniae*.

Later, the Applicant stated that the correlation of *Streptococcus pneumoniae* with clinical outcomes was not done due to the infrequency of a positive and lack of correlation with sputum culture results.

C. Clinical Trials

1. Protocol Study A0661013:

General Information:

Pfizer Central Research contracted principal investigators to conduct the study under its direction and in accordance with the protocol A0661013.

Globally, 76 sites (44 U.S.; 6 each for Canada, Argentina, Brazil, and India; 4 Chile; 3 South Africa; 1 Costa Rica) were filed to the IND and received study drug

An outside organization, _____ was contracted to monitor U.S. sites. International sites were monitored by staff employed by Pfizer's International Clinical Research Group (ICRG).

The final analysis of efficacy and safety data was performed by the Applicant, and the study report was prepared by the Applicant.

All double blind clinical supplies used in this trial were provided by the Applicant. For the U.S., Canada and Costa Rica, supplies were packaged and shipped directly from Groton to the sites. Supplies for other countries were shipped from Groton to a local Pfizer depot for further distribution to sites.

Study Design and Plan

Purpose of the Study:

For the indication "Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease (ABECB) in Adults", the applicant proposed 3 days azithromycin dosing (500 mg/day), 1500 mg total, as an alternative to 5 Days dosing (500 mg on day 1, followed by 250 mg on days 2-5), also 1500 mg total

The Applicant used a new 500 mg azithromycin film-coated tablet.

Study Dates: November 30, 1999 – September 16, 2000

Study Objectives:

The primary objective of this study was to test the hypothesis that azithromycin administered once daily as an oral dose of 500 mg/day for 3 days has an efficacy equivalent to that of clarithromycin administered 500 mg orally twice a day for 10 days for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) in non-hospitalized adult subjects.

A secondary objective was to compare the safety and toleration of the regimens.

Evaluation Groups:

Randomized:

Azithromycin: 201
Clarithromycin: 206

Age / Gender: Subjects of either gender between the ages of 35 and 75 years.

Dosing / Duration:

Subjects were assigned to receive either oral azithromycin 500 mg/day as a single daily dose for 3 days or oral clarithromycin 1000 mg/day divided as 500 mg morning and evening for 10 days.

Dosage Form: Azithromycin 500 mg tablet, lot N9063-G1; Azithromycin placebo, lot ED-O-074-297; and Clarithromycin 500 mg tablet, lot ED-O-372-899; and Clarithromycin placebo, lot ED-O-376-899.

Study Population:

Some Clinical / Bacteriologic Inclusion Criteria:

- Patient had a medical history of chronic bronchitis, as defined by the presence of a persistent cough with sputum production on most days of the month during three consecutive months for > 2 successive years.
- A clinical diagnosis of an acute bacterial exacerbation of chronic bronchitis. This diagnosis was based upon the presence of:
 - Increased sputum production compared to pre-exacerbation status

- The presence of purulent sputum defined as >25 white blood cells (WBC) per field and <10 squamous epithelial cells at 100x magnification (low power, 10x objective) microscopic examination
- Sputum Gram stain indicative of a bacterial pathogen
- A chest x-ray within 48 hours prior to first visit that excluded the diagnosis of pneumonia.

Some Clinical / Microbiology Exclusion Criteria:

- Known or suspected hypersensitivity or intolerance to azithromycin, clarithromycin, erythromycin, or other macrolides.
- Treatment with any systemic antibacterial within the previous 7 days.

Efficacy Assessments:

Clinical:

- Visit 1: Baseline
- Visit 2: End-of-Therapy (EOT), Day 10-12; and
- Visit 3: Test-of-Cure (TOC), Day 21-24, "Primary Endpoint"

Bacteriologic:

- Visit 1 Baseline:

Freshly expectorated sputum samples were examined macroscopically for consistency and color and microscopically to determine suitability for culture. Specimens were considered to be suitable if > 25 WBC and < 10 squamous cells were present per low power (100x) field of Gram stained specimen. Adequate specimens were submitted for culture with Gram stains to an approved local laboratory. The Gram stains and any culture isolates from the local laboratories were sent to the central laboratory to verify adequacy of Gram stain and to confirm the identification of the bacteria. The central laboratory also conducted susceptibility testing for azithromycin and clarithromycin on all respiratory pathogens. When available, results from the central laboratory were used for all reporting.

Blood cultures were obtained on febrile subjects at the discretion of the investigator. These cultures were for the clinical management of the subject and were not in lieu of sputum samples.

Serum was obtained and stored at the central laboratory for possible serological testing for *Mycoplasma pneumoniae*, *Legionella* spp. and *Chlamydia pneumoniae*. Urine specimens were obtained for the Binax NOW® Streptococcus pneumoniae antigen test which was performed at the study site.

- Visit 2: End-of-Therapy (EOT), Day 10-12 and Visit 3: Test-of-Cure (TOC), Day 21-24, "Primary Endpoint":

Sputum was obtained again on Visit 2 and Visit 3 and was examined microscopically for adequacy as was done at Visit 1. The Gram stained slides as well as culture isolates from the local laboratory were sent to the central laboratory for confirmation and susceptibility

testing. The absence of an adequate sputum specimen and the reason were documented. If a follow-up visit was required after Visit 3, sputum was obtained and processed as in Visit 2 and visit 3.

Serum was obtained at Visit 3 and stored at the central laboratory for possible serological testing for *Mycoplasma pneumoniae*, *Legionella* spp. and *Chlamydia pneumoniae*.

Efficacy Analysis:

Analyses were done on 2-populations:

- (1) Primary Efficacy: a modified intent-to-treat (MITT) group which included subjects who had taken at least one dose of study medication, had a confirmed diagnosis of acute bacterial exacerbation of chronic bronchitis and had a baseline purulent sputum, i.e., WBC > 25; and
- (2) Secondary Efficacy: a per-protocol (PP) evaluable subgroup which included MITT subjects that had received 80-120% of protocol specified doses of active therapy and had visits in the appropriate time windows. Both the clinical MITT and clinical PP evaluable subgroups had bacteriological subsets that had positive baseline sputum cultures for *Haemophilus influenzae*, or *Moraxella catarrhalis*, *Streptococcus pneumoniae* or *Haemophilus parainfluenzae*.

Clinical Outcome: At TOC the Applicant's clinical outcomes were cure and failure.

Bacteriological Outcome:

Bacteriological outcome was assessed on a by-subject basis as well as on a by-pathogen basis. Bacteriological outcome refers to the by-subject basis, and pathogen outcome refers to the by-pathogen basis.

For identification of the respiratory pathogens *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*, both the central and local laboratory results were used.

A purulent sputum culture was defined as providing a Gram stain with > 25 WBCs per LPF (low power field).

The By-Subject Bacteriological Outcomes were:

- Eradication:
No trace of any respiratory pathogen in purulent sputum culture and Applicant clinical outcome was not failure (unless the sputum culture demonstrated eradication on the same day as Applicant clinical outcome failure in which case it was classified as eradication).
- Presumed Eradication:
No sputum culture due to the subject not being able to expectorate or a nonpurulent sputum culture and Applicant clinical outcome was cure or improvement.
- Persistence:

A baseline respiratory pathogen still present in sputum culture

- Presumed Persistence:
Applicant clinical outcome was failure (unless a sputum culture demonstrated eradication on the same day as Applicant clinical outcome failure in which case it was classified as eradication).
- Superinfection:
Baseline respiratory pathogens gone but another respiratory pathogen present in sputum culture.
- Not Available (NA):
No sputum culture (including "not done" or missing for other reasons except for not being able to expectorate) and clinical outcome was not failure
- If a by-subject bacteriological outcome was both persistence and superinfection, the persistence outcome was used.

The pathogen outcomes were the same as the by-subject with the exceptions:

- Superinfection was not possible.
- The sputum culture results in the above definitions applied only to the pathogen of interest. Pathogen outcome was summarized separately for each baseline respiratory pathogen.

The sample size in the by-subject analysis was the number of bacteriologically evaluable subjects. The sample size in the by-pathogen analysis was larger than the number of bacteriologically evaluable subjects as some subjects had multiple pathogens.

The by-subject bacteriological outcome was summarized separately for each baseline respiratory pathogen and each geographical region.

2. General Comments

- The following 3-clinical investigators are excluded from the Clinical and Microbiology datasets analyses as the result of the Division of Investigation's (DSI) concern and recommendation on "Data Integrity": 1)

respectively. Therefore, the following 3 Clinical Investigator's, with their corresponding Patients' Identification Numbers, are not used in the following Microbiologist's dataset analyses:

- Microorganisms: *Haemophilus influenzae* isolates grouped; *Moraxella catarrhalis* isolates grouped; *Streptococcus pneumoniae* isolates grouped; and *Haemophilus parainfluenzae*

isolates .

- At this time, the clinical bacteriological analyses of the study datasets will concern only azithromycin.
- *Haemophilus parainfluenzae* is not a targeted microorganism in this study.

TABLES 3 - 10 show the results of Protocol A0661013: "A Randomized, Multicenter, Double-Blind, Double-Dummy Trial Comparing Azithromycin 500 mg Daily for 3 Days with Clarithromycin 1 Gram Daily for 10 Days for the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis" for the Modified-to-Treat (MITT) Population.

TABLE 3

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organisms Isolated	Azithromycin		Clarithromycin		Clinical Zone	Pathogen Outcome	Sputum Taken	Local		Central				
						S/I/R	MIC	S/I/R	MIC				WBC*	SEC*	Sac*	Grm*	WBC*	SEC*	
205	CLARI	BL	1		H. influenzae							Yes	>25	<10	Yes	Yes	>25	<10	
205	CLARI	NOT	15		H. influenzae					IMP	E	Yes	>25	<10			NA	NA	
205	CLARI	TOC	26		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
209	CLARI	BL	1		H. influenzae							Yes	>25	<10	Yes	Yes	>25	<10	
209	CLARI	NOT	12		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
209	CLARI	TOC	20		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
210	AZITH	BL	1		H. influenzae	5	1	25	5	4	20		Yes	>25	<10	Yes	Yes	>25	<10
210	AZITH	NOT	12		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
210	AZITH	TOC	21		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
318	CLARI	BL	1		H. influenzae	5	1	18	5	8	14		Yes	>25	<10	Yes	Yes	>25	<10
318	CLARI	NOT	13		H. influenzae					IMP	PE	UTE	NA	NA			NA	NA	
318	CLARI	TOC	22		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
319	CLARI	BL	1		H. influenzae	5	1	18	5	4	14		Yes	>25	<10	Yes	Yes	>25	<10
319	CLARI	NOT	11		H. influenzae					IMP	PE	UTE	<-25	>>10			NA	NA	
319	CLARI	TOC	22		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
332	AZITH	BL	1		H. influenzae	5	1	20	5	8	15		Yes	>25	<10	Yes	Yes	>25	<10
332	AZITH	NOT	11		H. influenzae					FAIL	E	Yes	>25	<10			NA	NA	
332	AZITH	TOC			H. influenzae					FAIL	PP	NA	NA	NA			NA	NA	
375	CLARI	BL	1		H. influenzae							Yes	>25	<10	Yes	Yes	>25	<10	
375	CLARI	NOT	11		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
375	CLARI	TOC	22		H. influenzae					CURE	PE	UTE	NA	NA			NA	NA	
185	AZITH	BL	1		M. catarrhalis							Yes	>25	<10	Yes	Yes	NA	NA	
185	AZITH	NOT	13		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
185	AZITH	TOC	22		M. catarrhalis					CURE	NA	UTE	NA	NA			NA	NA	
186	CLARI	BL	1		M. catarrhalis	5	<=0.06	39	5	0.12	35		Yes	>25	<10	Yes	Yes	NA	>>10
186	CLARI	NOT	14		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
186	CLARI	TOC	23		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
187	AZITH	BL	1		M. catarrhalis	5	<=0.06	38	5	<=0.06	33		Yes	>25	<10	Yes	Yes	>25	<10
187	AZITH	NOT	13		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
187	AZITH	TOC	19		M. catarrhalis					CURE	PE	Yes	<-25	>>10			NA	NA	
193	CLARI	BL	1		M. catarrhalis							Yes	>25	<10	Yes	Yes	>25	<10	
193	CLARI	NOT	13		M. catarrhalis					IMP	PE	UTE	NA	NA			NA	NA	
193	CLARI	TOC	22		M. catarrhalis					NA		UTE	NA	NA			NA	NA	
207	CLARI	BL	1		M. catarrhalis	5	<=0.06	43	5	<=0.06	40		Yes	>25	<10	Yes	Yes	>25	<10
207	CLARI	NOT	13		M. catarrhalis					IMP	PE	UTE	NA	NA			NA	NA	
207	CLARI	TOC	28		M. catarrhalis					FAIL	PP	Yes	>25	<10			NA	NA	
209	CLARI	BL	1		M. catarrhalis	5	<=0.06	25	5	<=0.06	16		Yes	>25	<10	Yes	Yes	>25	<10
209	CLARI	NOT	12		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
209	CLARI	TOC	20		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
213	AZITH	BL	1		M. catarrhalis	5	<=0.06	43	5	<=0.06	40		Yes	>25	<10	Yes	Yes	>25	<10
213	AZITH	NOT	12		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
213	AZITH	TOC	20		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
210	AZITH	BL	1		M. catarrhalis	5	<=0.06	33	5	<=0.06	30		Yes	>25	<10	Yes	Yes	<-25	>>10
210	AZITH	NOT	12		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
210	AZITH	TOC	22		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
217	AZITH	BL	1		M. catarrhalis	5	<=0.06	35	5	<=0.06	30		Yes	>25	<10	Yes	Yes	>25	<10
217	AZITH	NOT	12		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
217	AZITH	TOC	23		M. catarrhalis					CURE	PE	UTE	NA	NA			NA	NA	
223	AZITH	BL	1		M. catarrhalis	5	<=0.06	38	5	0.12	35		Yes	>25	<10	Yes	Yes	>25	<10
223	AZITH	NOT	1		M. catarrhalis							NA	NA	NA			NA	NA	
223	AZITH	TOC	1		M. catarrhalis							NA	NA	NA			NA	NA	
223	CLARI	BL	1		M. catarrhalis	5	<=0.06	41	5	<=0.06	59		Yes	>25	<10	Yes	Yes	>25	<10

TABLE 3 - Argentina (con't)

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organisms Isolated	Azithromycin			Clarithromycin			Clinical Outcome	Pathogen Outcome	Sputum Taken	Local		Central	
						S/I/R	MIC	Zone	S/I/R	MIC	Zone				WBC*	SEC*	Bac*	Grm*
	334	CLARI	BOT	11	M.catarrhalis							IMP	E	Yes	>25	<10	NA	NA
	334	CLARI	TOC	22	M.catarrhalis							CURE	E	Yes	>25	<10	NA	NA
	335	AZITH	BL	1	M.catarrhalis	S	<=0.06	41	S	<=0.06	39			Yes	>25	<10	Yes	Yes
	335	AZITH	EOT	13	M.catarrhalis							IMP	PE	UTE	NA	NA	NA	NA
	335	AZITH	TOC	21	M.catarrhalis							CURE	PE	UTE	NA	NA	NA	NA
	382	CLARI	BL	1	M.catarrhalis	S	<=0.06	40	S	<=0.06	36			Yes	>25	<10	Yes	Yes
	382	CLARI	EOT	13	M.catarrhalis							CURE	PE	UTE	NA	NA	NA	NA
	382	CLARI	TOC	43	M.catarrhalis							CURE	PE	UTE	NA	NA	NA	NA
	189	AZITH	BL	0	S.pneumoniae	S	0.12	26	S	0.03	30			Yes	>25	<10	Yes	Yes
	189	AZITH	EOT	11	S.pneumoniae							IMP	PE	UTE	NA	NA	NA	NA
	189	AZITH	TOC	21	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	190	CLARI	BL	1	S.pneumoniae									Yes	>25	<10	Yes	Yes
	190	CLARI	EOT	10	S.pneumoniae							IMP	PE	UTE	NA	NA	NA	NA
	190	CLARI	TOC	23	S.pneumoniae							FAIL	PP	UTE	NA	NA	NA	NA
	193	AZITH	BL	1	S.pneumoniae	S	0.12	26	S	0.03	31			Yes	>25	<10	Yes	Yes
	193	AZITH	EOT	14	S.pneumoniae							IMP	PE	Yes	<=25	>=10	NA	NA
	193	AZITH	TOC	27	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	194	CLARI	BL	1	S.pneumoniae	S	0.12	25	S	0.06	29			Yes	>25	<10	Yes	Yes
	194	CLARI	EOT	15	S.pneumoniae							IMP	E	Yes	>25	<10	NA	NA
	194	CLARI	TOC	25	S.pneumoniae									UTE	NA	NA	NA	NA
	201	CLARI	BL	1	S.pneumoniae									Yes	>25	<10	Yes	Yes
	201	CLARI	EOT	11	S.pneumoniae							IMP	PE	UTE	NA	NA	NA	NA
	201	CLARI	TOC	23	S.pneumoniae							CURE	PE	Yes	<=25	>=10	<=25	>=10
	202	CLARI	BL	1	S.pneumoniae	S	0.12	28	S	0.06	30			Yes	>25	<10	Yes	Yes
	202	CLARI	EOT	11	S.pneumoniae	S	0.25	26	S	0.06	28			Yes	>25	<10	NA	>=10
	202	CLARI	TOC	22	S.pneumoniae							CURE	E	Yes	>25	<10	>25	<10
	205	CLARI	BL	1	S.pneumoniae	S	0.12	28	S	0.03	30			Yes	>25	<10	Yes	Yes
	205	CLARI	EOT	15	S.pneumoniae							IMP	E	Yes	>25	<10	NA	NA
	205	CLARI	TOC	26	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	208	AZITH	BL	1	S.pneumoniae	S	0.06	41	S	0.016	43			Yes	>25	<10	Yes	Yes
	208	AZITH	EOT	14	S.pneumoniae							IMP	E	Yes	>25	<10	NA	NA
	208	AZITH	TOC	28	S.pneumoniae	S	0.06	28	S	0.03	32			Yes	>25	<10	>25	<10
	306	AZITH	BL	-1	S.pneumoniae							FAIL	P	Yes	>25	<10	Yes	Yes
	306	AZITH	EOT	12	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	306	AZITH	TOC	23	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	320	AZITH	BL	1	S.pneumoniae	S	0.06	34	S	0.03	38			Yes	>25	<10	Yes	Yes
	320	AZITH	EOT	11	S.pneumoniae							IMP	PE	UTE	NA	NA	NA	NA
	320	AZITH	TOC	23	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	321	AZITH	BL	1	S.pneumoniae	S	0.12	25	S	0.03	28			Yes	>25	<10	Yes	Yes
	321	AZITH	EOT	11	S.pneumoniae							IMP	E	Yes	>25	>=10	NA	>=10
	321	AZITH	TOC	32	S.pneumoniae							CURE	E	Yes	>25	<10	NA	NA
	322	CLARI	BL	1	S.pneumoniae	S	0.12	25	S	0.03	30			Yes	>25	<10	Yes	Yes
	322	CLARI	EOT	10	S.pneumoniae							IMP	E	Yes	>25	<10	NA	NA
	322	CLARI	TOC	24	S.pneumoniae							CURE	E	Yes	>25	<10	>25	<10
	324	CLARI	BL	1	S.pneumoniae	S	0.12	25	S	0.03	30			Yes	>25	<10	Yes	Yes
	324	CLARI	EOT	13	S.pneumoniae							IMP	PE	UTE	NA	NA	NA	NA
	324	CLARI	TOC	24	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	325	CLARI	BL	1	S.pneumoniae	R	16	9	R	6	10			Yes	>25	<10	Yes	Yes
	325	CLARI	EOT	11	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	325	CLARI	TOC	21	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	326	CLARI	BL	1	S.pneumoniae	S	0.06	36	S	0.016	40			Yes	>25	<10	Yes	Yes
	326	CLARI	EOT	11	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	326	CLARI	TOC	22	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	329	AZITH	BL	1	S.pneumoniae	S	0.12	36	S	0.03	38			Yes	>25	<10	Yes	Yes
	329	AZITH	EOT	13	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	329	AZITH	TOC	23	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA

* Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence

Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 – Modified-To-Treat (MITT) Population – Argentina

1. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2

Clinical Outcome:

Bacteriological Outcome:

Patients Cured = 1/2 (50%)
 Patient Failures = 1/2 (50%)

Presumed Eradicated = 1/2 (50%)

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

Clinical Outcome:

Patients Cured = 5/6 (83.3%)
 Not Given = 1/6 (16.7%)

Bacteriological Outcome:

Presumed Eradicated = 4/6 (66.7%)
 Result Not Available = 2/6 (33.3%)

3. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 7

Clinical Outcome:

Patients Cured = 6/7 (85.7%)
 Patient Failures = 1/7 (14.3%)

Bacteriological Outcome:

Eradicated = 1/7 (14.3%)
 Presumed Eradicated = 5/7 (71.4%)
 Eradicated + Presumed Eradicated = 6/7 (85.7%)

TABLE 4 - Brazil

Inv Base	Patient ID	Treat Group	Study Visit Day	Targeted Organisms Isolated	Azithromycin		Clarithromycin		Clinical Outcome	Pathogen Outcome	Sputum Taken	Local		Central						
					S/I/R	MIC	Zone	S/I/R				MIC	Zone	WBC*	SEC*	Bac*	Gr*	WBC*	SEC*	
	626	AZITH	BL	1	N.influenzae	S	1	22	S	0	14	IMP	PE	Yes	>25	<10	Yes	Yes	>25	<10
	626	AZITH	EOT	15	N.influenzae							CURE	PE	UTE	NA	NA			NA	NA
	626	AZITH	TOC	22	N.influenzae							CURE	PE	UTE	NA	NA			NA	NA
	628	CLARI	EOT	12	H.influenzae	S	2	20	I	16	12	IMP		Yes	>25	>=10			NA	NA
	628	CLARI	TOC	22	H.influenzae	S	2	18	I	16	12	CURE		Yes	>25	<10			>25	<10
	639	AZITH	BL	1	H.influenzae	S	1	20	I	16	12			Yes	>25	<10	Yes	Yes	>25	<10
	639	AZITH	EOT	12	H.influenzae							IMP	E	Yes	>25	<10			>25	<10
	639	AZITH	TOC	22	H.influenzae							CURE	E	Yes	>25	<10			>25	<10
	721	CLARI	BL	1	H.influenzae	S	1	26	S	0	18			Yes	>25	<10	Yes	Yes	>25	<10
	721	CLARI	EOT	11	H.influenzae							CURE	PE	UTE	NA	NA			NA	NA
	721	CLARI	TOC	21	H.influenzae							CURE	PE	UTE	NA	NA			NA	NA
	612	CLARI	BL	1	M.catarrhalis	S	<=0.06	35	S	<=0.06	32			Yes	>25	<10			<=25	NA
	612	CLARI	EOT	12	M.catarrhalis							IMP	E	Yes	>25	<10			<=25	NA
	612	CLARI	TOC	22	M.catarrhalis							CURE	PE	UTE	NA	NA			NA	NA
	624	AZITH	BL	1	M.catarrhalis									Yes	>25	<10	Yes	Yes	NA	>=10
	624	AZITH	EOT	1	M.catarrhalis									NA	NA	NA			NA	NA
	624	AZITH	TOC	20	M.catarrhalis							CURE	PE	Yes	<=25	>=10			NA	>=10
	630	CLARI	BL	1	M.catarrhalis	S	<=0.06	35	S	<=0.06	30			Yes	>25	<10	Yes	Yes	>25	<10
	630	CLARI	EOT	13	M.catarrhalis							CURE	PE	UTE	NA	NA			NA	NA
	630	CLARI	TOC	24	M.catarrhalis							CURE	PE	UTE	NA	NA			NA	NA
	631	CLARI	TOC	23	M.catarrhalis							FAIL		Yes	>25	<10			>25	<10
	635	CLARI	BL	1	M.catarrhalis									Yes	>25	<10	Yes	Yes	<=25	NA
	635	CLARI	EOT	11	M.catarrhalis							IMP	PE	Yes	<=25	<10			<=25	NA
	635	CLARI	TOC	21	M.catarrhalis							FAIL	PP	Yes	<=25	<10			>25	<10
	640	CLARI	BL	1	M.catarrhalis	S	<=0.06	33	S	<=0.06	30			Yes	>25	<10	Yes	Yes	>25	<10
	640	CLARI	EOT	12	M.catarrhalis							IMP	E	Yes	>25	>=10			NA	NA
	640	CLARI	TOC	26	M.catarrhalis							FAIL	E	Yes	>25	<10			>25	<10
	713	CLARI	BL	1	M.catarrhalis									Yes	>25	<10	Yes	Yes	>25	<10
	713	CLARI	EOT	14	M.catarrhalis							CURE	PE	Yes	<=25	>=10			NA	>=10
	724	AZITH	BL	1	M.catarrhalis	S	<=0.06	35	S	<=0.06	33			Yes	>25	<10	Yes	Yes	>25	<10
	724	AZITH	EOT	15	M.catarrhalis							CURE	E	Yes	>25	<10			>25	<10
	724	AZITH	TOC	22	M.catarrhalis							CURE	E	Yes	>25	<10			NA	>=10
	605	AZITH	BL	1	S.pneumoniae	S	0.12	25	S	0.03	29			Yes	>25	<10	Yes	Yes	>25	<10
	605	AZITH	EOT	13	S.pneumoniae							IMP	PE	Yes	<=25	>=10			NA	NA
	605	AZITH	TOC	24	S.pneumoniae							CURE	E	Yes	>25	<10			<=25	>=10
	608	CLARI	BL	1	S.pneumoniae	S	0.12	26	S	0.03	29			Yes	>25	<10	Yes	Yes	>25	<10
	608	CLARI	EOT	13	S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
	608	CLARI	TOC	22	S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
	610	AZITH	BL	1	S.pneumoniae	S	0.06	28	S	0.03	30			Yes	>25	<10	Yes	Yes	>25	<10
	610	AZITH	EOT	11	S.pneumoniae							IMP	E	Yes	>25	<10			<=25	NA
	610	AZITH	TOC	26	S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
	624	AZITH	BL	1	S.pneumoniae									Yes	>25	<10	Yes	Yes	NA	>=10
	624	AZITH	EOT	1	S.pneumoniae									NA	NA	NA			NA	NA
	624	AZITH	TOC	20	S.pneumoniae							CURE	PE	Yes	<=25	>=10			NA	>=10
	628	CLARI	BL	1	S.pneumoniae	S	0.06	28	S	0.016	32			Yes	>25	<10	Yes	Yes	>25	<10
	628	CLARI	EOT	12	S.pneumoniae							IMP	E	Yes	>25	>=10			NA	NA
	628	CLARI	TOC	23	S.pneumoniae							CURE	E	Yes	>25	<10			>25	<10
	631	CLARI	BL	1	S.pneumoniae									Yes	>25	<10	Yes	Yes	>25	<10
	631	CLARI	EOT	12	S.pneumoniae							CURE	E	Yes	>25	<10			>25	<10
	631	CLARI	TOC	23	S.pneumoniae							FAIL	E	Yes	>25	<10			>25	<10
	632	AZITH	BL	1	S.pneumoniae	S	0.06	30	S	0.016	35			Yes	>25	<10	Yes	Yes	NA	>=10
	632	AZITH	EOT	15	S.pneumoniae							CURE	PE	Yes	<=25	<10			NA	NA

APPEARS THIS WAY
 ON ORIGINAL

TABLE 4 - Brazil (con't)

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organisms Isolated	Azithromycin			Clarithromycin			Clinical Outcome	Pathogen Outcome	Sputum Taken	Local			Central	
						S/I/R	MIC	Zone	S/I/R	MIC	Zone				WBC*	SEC*	Bac*	Grm*	WBC*
	832	AZITH	TOC	25	S.pneumoniae	S	0.06	21 S	0.03	25	CURE	PE	Yes	<=25	>=10		NA	NA	
	840	CLARI	TOC	26	S.pneumoniae	S	0.06	21 S	0.03	25	FAIL		Yes	>25	<10		>25	<10	
	733	CLARI	BL	1	S.pneumoniae	S	0.06	25 S	0.03	28			Yes	>25	<10	Yes	Yes	<=25	NA
	733	CLARI	EOT	10	S.pneumoniae						CURE	PE	UTE	NA	NA		NA	NA	
	733	CLARI	TOC	24	S.pneumoniae						CURE	PE	UTE	NA	NA		NA	NA	
	737	AZITH	BL	1	S.pneumoniae	S	0.12	26 S	0.03	30			Yes	>25	<10	Yes	Yes	>25	<10
	737	AZITH	EOT	11	S.pneumoniae						IMF	PE	Yes	<=25	>=10		NA	NA	
	737	AZITH	TOC	21	S.pneumoniae						CURE	S	Yes	>25	<10		>25	<10	

Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence
 Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 -- Modified-To-Treat (MITT) Population -- Brazil

1. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2

Clinical Outcome:

Patients Cured = 2/2 (100%)

Bacteriological Outcome:

Eradicated = 1/2 (50%)
 Presumed Eradicated = 1/2 (50%)
 Eradicated + Presumed Eradicated = 2/2 (100%)

2. Number of Patients isolated with *Moraxella catarrhalis* at Baseline = 2

Clinical Outcome:
Patients Cured = 2/2 (100%)

Bacteriological Outcome:
Presumed Eradicated = 2/2 (100%)

3. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 5

Clinical Outcome:
Patients Cured = 5/5 (100%)

Bacteriological Outcome:
● Eradicated = 1/5 (20%)
Presumed Eradicated = 4/5 (80%)
Eradicated + Presumed Eradicated = 5/5 (100%)

APPEARS THIS WAY
ON ORIGINAL

TABLE 5* – Canada

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organisms Isolated	Azithromycin			Clarithromycin			Clinical Outcome	Pathogen Outcome	Sputum Taken	Local			Central				
						S/I/R	MIC	Zone	S/I/R	MIC	Zone				WBC*	SEC*	Bac*	Grm*	WBC*	SEC*	Bac*	Grm*
	579	AZITH	BL	1	S.pneumoniae											Yes	>25	<10	Mo	Yes	>25	<10
	579	AZITH	BOT	14	S.pneumoniae							CURE	E			Yes	>25	<10			>25	<10
	579	AZITH	TOC	23	S.pneumoniae							CURE	PE			UTE	NA	NA			NA	NA

* Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence
 Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 -- Modified-To-Treat (MITT) Population -- Canada

1. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 1

Clinical Outcome:
 Patients Cured = 1/1 (100%)

Bacteriological Outcome:
 Presumed Eradicated = 1/1 (100%)

APPEARS THIS WAY
 ON ORIGINAL

TABLE 6* – Chile

Inv Name	Patient ID	Treat Group	Study Visit Day	Targeted Organism Isolated	Azithromycin		Clarithromycin		Clinical Outcome	Pathogen Outcome	Sputum Taken	Local		Central				
					S/I/R	MIC	Zone	S/I/R				MIC	Zone	WBC*	SEC*	Bac*	Grm*	WBC*
	411	AZITH	BL	1	H.influenzae	S	1	23	6	4	16	Yes	>25	<10	Yes	Yes	>25	<10
	411	AZITH	BOT	10	H.influenzae							UTE	NA	NA			NA	NA
	411	AZITH	TOC	22	H.influenzae							UTE	NA	NA			NA	NA
	422	AZITH	BL	1	H.influenzae	S	0.5	25	6	4	18	Yes	>25	<10	Yes	Yes	>25	<10
	422	AZITH	BOT	10	H.influenzae							IMP	PE	UTE	NA	NA	NA	NA
	422	AZITH	TOC	21	H.influenzae							UTE	NA	NA			NA	NA
	424	CLARI	BL	1	H.influenzae	S	2	23	5	8	15	Yes	>25	<10	Yes	Yes	NA	>10
	424	CLARI	BOT	1	H.influenzae							NA	NA	NA			NA	NA
	424	CLARI	TOC	1	H.influenzae							NA	NA	NA			NA	NA
	423	AZITH	BL	1	M.catarrhalis	S	<=0.06	38	5	0.12	34	Yes	>25	<10	Yes	Yes	>25	<10
	423	AZITH	BOT	11	M.catarrhalis							UTE	NA	NA			NA	NA
	423	AZITH	TOC	23	M.catarrhalis							UTE	NA	NA			NA	NA
	409	AZITH	BL	1	S.pneumoniae	S	0.06	27	5	0.03	25	Yes	>25	<10	Yes	Yes	>25	<10
	409	AZITH	BOT	12	S.pneumoniae							IMP	PE	UTE	NA	NA	NA	NA
	409	AZITH	TOC	23	S.pneumoniae							CURE	Z	Yes	>25	<10	>25	<10
	410	CLARI	BL	1	S.pneumoniae	S	0.06	24	5	0.03	25	Yes	>25	<10	Yes	Yes	>25	<10
	410	CLARI	BOT	12	S.pneumoniae							CURE	E	Yes	>25	NA	>25	<10
	410	CLARI	TOC	23	S.pneumoniae							FAIL	E	Yes	>25	>=10	>25	<10
	411	AZITH	BL	1	S.pneumoniae	S	0.06	25	5	0.03	28	Yes	>25	<10	Yes	Yes	>25	<10
	411	AZITH	BOT	10	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	411	AZITH	TOC	22	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	428	AZITH	BL	1	S.pneumoniae	S	0.06	25	5	0.03	28	Yes	>25	<10	Yes	Yes	>25	<10
	428	AZITH	BOT	10	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	428	AZITH	TOC	22	S.pneumoniae							CURE	PE	UTE	NA	NA	NA	NA
	426	CLARI	BL	1	H.parsinfluenzae	S	4	20	R	32	10	Yes	>25	<10	Yes	Yes	>25	<10
	426	CLARI	BOT	12	H.parsinfluenzae							CURE	PE	UTE	NA	NA	NA	NA

* Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence
 Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 -- Modified-To-Treat (MITT) Population -- Chile

1. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 2

Clinical Outcome: Patients Cured = 2/2 (100%)
Bacteriological Outcome: Presumed Eradicated = 2/2 (100%)

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

Clinical Outcome: Patients Cured = 1/1 (100%)
Bacteriological Outcome: Presumed Eradicated = 1/1 (100%)

3. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 3

Clinical Outcome: Patients Cured = 3/3 (100%)
Bacteriological Outcome:
 Eradicated = 1/3 (33.3%)
 Presumed Eradicated = 2/3 (66.7%)
 Eradicated + Presumed Eradicated = 3/3 (100%)

TABLE 7 - Costa Rica

NDA 50-784
 PFIZER INC.
 ZITHROMAX® (azithromycin) 500 mg Film-Coated Tablet

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organisms Isolated	Azithromycin		Clarithromycin		Clinical Outcome	Pathogen	Sputum Taken	Local		Bac*	Grm*	Central			
						S/I/R	MIC	Zone	S/I/R				MIC	Zone			WBC*	SEC*	WBC*	SEC*
349	CLARI	BL	1		H.influenzae	S	1	18	S	8	14	CURE	PE	Yes	>25	<10	Yes	Yes	NA	>=10
349	CLARI	BOT	11		H.influenzae							CURE	PE	Yes	<=25	>=10			NA	NA
349	CLARI	TOC	22		H.influenzae							CURE	PE	Yes	<=25	>=10			NA	NA
354	AZITH	BL	1		H.influenzae	S	1	23	S	8	14	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
354	AZITH	BOT	11		H.influenzae							CURE	PE	Yes	<=25	>=10			NA	NA
354	AZITH	TOC	24		H.influenzae							CURE	PE	Yes	<=25	>=10			NA	NA
169	CLARI	BL	1		S.pneumoniae	S	0.12	26	S	0.06	31	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
169	CLARI	BOT	12		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
169	CLARI	TOC	24		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
170	AZITH	BL	1		S.pneumoniae	S	0.12	26	S	0.06	30	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
170	AZITH	BOT	11		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
170	AZITH	TOC	21		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
171	CLARI	BL	0		S.pneumoniae	S	0.12	20	S	0.06	32	CURE	PE	Yes	>25	<10	Yes	Yes	NA	>=10
171	CLARI	BOT	10		S.pneumoniae							FAIL	PP	Yes	<=25	>=10			NA	NA
171	CLARI	TOC			S.pneumoniae							FAIL	PP	NA	NA			NA	NA	
173	AZITH	BL	1		S.pneumoniae	S	0.12	27	S	0.06	32	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
173	AZITH	BOT	10		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
173	AZITH	TOC	22		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
174	AZITH	BL	1		S.pneumoniae	S	0.12	26	S	0.06	30	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
174	AZITH	BOT	10		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
174	AZITH	TOC	14		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
175	CLARI	BL	1		S.pneumoniae	S	0.12	28	S	0.06	32	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
175	CLARI	BOT	12		S.pneumoniae							IMP	PE	UTE	NA	NA			NA	NA
175	CLARI	TOC	22		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
176	CLARI	BL	1		S.pneumoniae	S	0.12	25	S	0.06	28	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
176	CLARI	BOT	11		S.pneumoniae							IMP	PE	UTE	NA	NA			NA	NA
176	CLARI	TOC	25		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
177	AZITH	BL	1		S.pneumoniae	S	0.12	24	S	0.06	30	CURE	PE	Yes	>25	<10	Yes	Yes	<=25	NA
177	AZITH	BOT	11		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
177	AZITH	TOC	22		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
179	AZITH	BL	1		S.pneumoniae	S	0.12	28	S	0.06	32	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
179	AZITH	BOT	10		S.pneumoniae							IMP	PE	Yes	<=25	>=10			NA	NA
179	AZITH	TOC	22		S.pneumoniae							CURE	PE	Yes	<=25	>=10			NA	NA
180	CLARI	BL	1		S.pneumoniae	S	0.12	25	S	0.03	30	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
180	CLARI	BOT	10		S.pneumoniae							IMP	PE	UTE	NA	NA			NA	NA
180	CLARI	TOC	22		S.pneumoniae							CURE	PE	Yes	<=25	<10			NA	NA
181	AZITH	BL	1		S.pneumoniae	S	0.06	25	S	0.03	27	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
181	AZITH	BOT	12		S.pneumoniae							IMP	PE	Yes	<=25	>=10			NA	NA
181	AZITH	TOC	21		S.pneumoniae							FAIL	PP	Yes	<=25	>=10			NA	NA
182	CLARI	BL	1		S.pneumoniae	S	0.12	24	S	0.03	28	CURE	PE	Yes	>25	<10	Yes	Yes	<=25	>=10
182	CLARI	BOT	11		S.pneumoniae							IMP	PE	Yes	<=25	<10			NA	NA
182	CLARI	TOC	24		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
183	AZITH	BL	1		S.pneumoniae	S	0.12	25	S	0.03	28	CURE	PE	Yes	>25	<10	Yes	Yes	<=25	>=10
183	AZITH	BOT	10		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
183	AZITH	TOC	23		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
184	CLARI	BL	1		S.pneumoniae	S	0.12	27	S	0.03	30	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
184	CLARI	BOT	10		S.pneumoniae							IMP	PE	UTE	NA	NA			NA	NA
184	CLARI	TOC	22		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
185	AZITH	BL	1		S.pneumoniae	S	0.12	29	S	0.03	31	CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10
185	AZITH	BOT	10		S.pneumoniae							IMP	PE	UTE	NA	NA			NA	NA
185	AZITH	TOC	23		S.pneumoniae							CURE	PE	UTE	NA	NA			NA	NA
186	CLARI	BL	1		S.pneumoniae							CURE	PE	Yes	>25	<10	Yes	Yes	>25	<10

APPEARS THIS WAY
 ON ORIGINAL

TABLE 7 - Costa Rica (con't)

ZITHROMAX® (azithromycin) 500 mg Film-Coated Tablet

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organisms Isolated	Azithromycin		Clarithromycin		Clinical Zone	Pathogen Outcome	Sputum Taken	Local			Central			
						E/I/R	MIC	Zone	S/I/R				MIC	Zone	WBC*	SEC*	Bac*	Grm*	WBC*
	346	CLARI	EOT	10	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	346	CLARI	TOC	22	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	347	AZITH	BL	1	S.pneumoniae	S	0.12	20	S	0.03	24		Yes	>25	<10	Yes	Yes	>25	<10
	347	AZITH	EOT	12	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	347	AZITH	TOC	21	S.pneumoniae						CURE	PE	Yes	<=25	>=10			NA	NA
	348	CLARI	BL	1	S.pneumoniae	S	0.12	28	S	0.03	31		Yes	>25	<10	Yes	Yes	>25	<10
	348	CLARI	EOT	12	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	348	CLARI	TOC	21	S.pneumoniae						CURE	PE	Yes	<=25	>=10			NA	NA
	350	CLARI	BL	1	S.pneumoniae	F	0.06	25	S	0.03	28		Yes	>25	<10	Yes	Yes	<=25	NA
	350	CLARI	EOT	12	S.pneumoniae						IMP	PE	UTE	NA	NA	NA	NA		
	350	CLARI	TOC	23	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	351	AZITH	BL	1	S.pneumoniae	S	0.12	26	S	0.03	29		Yes	>25	<10	Yes	Yes	NA	>=10
	351	AZITH	EOT	11	S.pneumoniae						IMP	PE	UTE	NA	NA	NA	NA		
	351	AZITH	TOC	23	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	352	AZITH	BL	1	S.pneumoniae								Yes	>25	<10	Yes	Yes	<=25	>=10
	352	AZITH	EOT	12	S.pneumoniae						FAIL	PP	Yes	<=25	>=10			NA	NA
	352	AZITH	TOC	20	S.pneumoniae						FAIL	PP	UTE	NA	NA	NA	NA		
	353	AZITH	BL	1	S.pneumoniae	S	0.12	24	S	0.03	28		Yes	>25	<10	Yes	Yes	>25	<10
	353	AZITH	EOT	11	S.pneumoniae						IMP	PE	Yes	<=25	>=10			NA	NA
	353	AZITH	TOC	24	S.pneumoniae						CURE	PE	Yes	<=25	>=10			NA	NA
	355	CLARI	BL	1	S.pneumoniae	S	0.12	24	S	0.03	28		Yes	>25	<10	Yes	Yes	NA	>=10
	355	CLARI	EOT	10	S.pneumoniae						IMP	PE	Yes	<=25	>=10			NA	NA
	355	CLARI	TOC	21	S.pneumoniae						CURE	PE	Yes	<=25	>=10			NA	NA
	361	AZITH	BL	1	S.pneumoniae	S	0.12	21	S	0.03	28		Yes	>25	<10	Yes	Yes	<=25	>=10
	361	AZITH	EOT	10	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	361	AZITH	TOC	21	S.pneumoniae						CURE	PE	Yes	<=25	>=10			NA	NA
	362	AZITH	BL	1	S.pneumoniae	S	0.12	21	S	0.03	28		Yes	>25	<10	Yes	Yes	<=25	>=10
	362	AZITH	EOT	11	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	362	AZITH	TOC	21	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	363	CLARI	BL	1	S.pneumoniae	S	0.12	25	S	0.03	25		Yes	>25	<10	Yes	Yes	NA	NA
	363	CLARI	EOT	13	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		
	363	CLARI	TOC	22	S.pneumoniae						CURE	PE	UTE	NA	NA	NA	NA		

* Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence
 Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 -- Modified-To-Treat (MITT) Population -- Costa Rica

1. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 1

Clinical Outcome:

Patients Cured = 1/1 (100%)

Bacteriological Outcome:

Presumed Eradicated = 1/1 (100%)

2. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 15

Clinical Outcome:

Patients Cured = 13/15 (86.7%)

Patients Failed = 2/15 (13.3%)

Bacteriological Outcome:

Presumed Eradicated = 13/15 (86.7%)

TABLE 8* - India

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Targeted Organism Isolated	Azithromycin		Clarithromycin		Clinical Outcome	Pathogen Outcome	Sputum Taken	Local		Central				
						S/I/R	MIC	Zone	S/I/R				MIC	Zone	WBC*	SEC*	Bac*	Grm*	WBC*
	649	CLARI	BL	1	H.influenzae	S	1	30	S	8	15		Yes	>25	<10	Yes	Yes	>25	<10
	649	CLARI	BOT	11	H.influenzae	S	1	19	S	8	14	IMP	P	Yes	>25	>=10	MA	>=10	
	649	CLARI	TOC	22	H.influenzae	S	1					CURE	PE	Yes	<=25	<10		>25	<10
	673	CLARI	BL	1	M.catarrhalis								Yes	>25	<10	No	Yes	NA	>=10
	673	CLARI	BOT	11	M.catarrhalis							CURE	PE	UTE	NA	NA	NA	NA	NA
	673	CLARI	TOC	21	M.catarrhalis							CURE	PE	UTE	NA	NA	NA	NA	NA
	674	CLARI	BL	1	M.catarrhalis	S	<=0.06	35	S	<=0.06	34		Yes	>25	<10	No	Yes	>25	<10
	674	CLARI	BOT	11	M.catarrhalis							IMP	E	Yes	>25	<10	NA	>=10	
	674	CLARI	TOC	21	M.catarrhalis							CURE	PE	UTE	NA	NA	NA	NA	NA
	669	AZITH	BL	1	S.pneumoniae								Yes	>25	<10	Yes	Yes	>25	<10
	669	AZITH	BOT	12	S.pneumoniae							CURE	PE	Yes	<=25	<10	NA	>=10	
	669	AZITH	TOC	21	S.pneumoniae							CURE	E	Yes	<=25	<10		>25	<10
	651	AZITH	BL	1	H.parainfluenzae	S	2	18	I	16	12		Yes	>25	<10	Yes	Yes	NA	>=10
	651	AZITH	BOT	11	H.parainfluenzae							IMP	PE	Yes	<=25	>=10		>25	<10
	651	AZITH	TOC	21	H.parainfluenzae	S	2	19	I	16	12	CURE	P	Yes	<=25	<10		>25	<10
	669	AZITH	BL	1	H.parainfluenzae	S	1	16	S	8	13		Yes	>25	<10	Yes	Yes	>25	<10
	669	AZITH	BOT	12	H.parainfluenzae							CURE	PE	Yes	<=25	<10	NA	>=10	
	669	AZITH	TOC	21	H.parainfluenzae							CURE	E	Yes	>25	<10		>25	<10

Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence
 Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 -- Modified-To-Treat (MITT) Population -- India

1. Number of patients isolated with *Streptococcus pneumoniae* at baseline = 1

<u>Clinical Outcome:</u> Patients Cured = 1/1 (100%)	<u>Bacteriological Outcome:</u> Eradicated = 1/1 (100%)
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2. Number of patients isolated with *Haemophilus parainfluenzae* at baseline = 2

<u>Clinical Outcome:</u> Patients Cured = 2/2 (100%)	<u>Bacteriological Outcome:</u> Eradicated = 1/2 (50%)
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TABLE 9 - South Africa

APPEARS THIS WAY
 ON ORIGINAL

Inv Name	Patient ID	Treat Group	Study Visit	Study Day	Organisms Isolated	Azithromycin		Clarithromycin		Clinical Pathogen Outcome	Sputum Outcome	Local		Central						
						E/S/R	MIC	Zone	E/S/R			MIC	Zone	WBC*	SEC*	Bac*	Grm*	WBC*	SEC*	
513	CLARI	BL	1		H.influenzae	S	0.5	28	8	4	19	Yes	>25	<10	Yes	Yes	>25	<10		
513	CLARI	EOT	12		H.influenzae	S	1	23	8	8	14	IMP	P	Yes	>25	>=10	NA	>=10		
513	CLARI	TOC	22		H.influenzae	S	1	25	8	8	13	CURE	P	Yes	<=25	<10	>25	<10		
515	AZITH	BL	1		H.influenzae	S	1	26	8	8	20	IMP	P	Yes	>25	<10	Yes	Yes	>25	<10
515	AZITH	EOT	11		H.influenzae	S	1	22	8	8	18	IMP	P	Yes	<=25	<10	>25	<10		
515	AZITH	TOC	21		H.influenzae	S	1	21	8	8	14	CURE	P	Yes	>25	<10	>25	<10		
516	CLARI	BL	1		H.influenzae	S	2	23	1	16	12			Yes	>25	<10	Yes	Yes	>25	<10
516	CLARI	EOT	14		H.influenzae							CURE	PE	UTE	NA	NA	NA	NA		
516	CLARI	TOC	23		H.influenzae							CURE	PE	UTE	NA	NA	NA	NA		
514	AZITH	BL	1		H.parainfluenzae	S	2	22	1	16	11			Yes	>25	<10	Yes	Yes	>25	<10
514	AZITH	EOT	12		H.parainfluenzae	S	2	22	1	16	11	CURE	P	Yes	<=25	<10	NA	NA		
514	AZITH	TOC	22		H.parainfluenzae							CURE	PE	UTE	NA	NA	NA	NA		

* Adopted from NDA 50-784, Letter Date: 01/18/02, Enclosure 2, FDA Query #15.

Treatment Group: Azith = Azithromycin, Clari = Clarithromycin
 Pathogen Outcome: E = Eradication, P = Persistence, SI = Superinfection, PE = Presumed Eradication, and PP = Presumed Persistence
 Clinical Outcome: C = Cure, Imp = Improved, and F = Fail. UTE: Unable to Expectorate
 * WBC = Gram Stain: WBC PER LPF (10X), SEC = Gram Stain: SQUAM EPITHELIAL CELLS/LPF (10X)
 * Bac = BACTERIAL ORGANISM PRESENT, Grm = GRAM STAIN SENT TO CENTRAL LAB

Clinical Outcome and Bacteriological Outcome Results at TOC

Protocol: A0661013 -- Modified-To-Treat (MITT) Population -- South Africa

1. Number of Patients isolated with *Haemophilus influenzae* at Baseline = 1

Clinical Outcome:

Patients Cured = 1/1 (100%)

Bacteriological Outcome:

Not E or PE

2. Number of patients isolated with *Haemophilus parainfluenzae* at baseline = 1

Clinical Outcome:

Patients Cured = 1/1 (100%)

Bacteriological Outcome:

Presumed Eradicated = 1/1 (100%)

APPEARS THIS WAY
 ON ORIGINAL