

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**50-784 / S-004, S-006**

**MICROBIOLOGY REVIEW**

**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)**  
**Clinical Microbiological Review of Efficacy Supplement**

**NDA#:** 50-784                      **REVIEW #:** 1                      **COMPLETED DATE:** 12/16/03  
(NDAs 50-710 & 50-711 referenced for labeling.)

**Reviewer:** Harold V. Silver

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
50-784/SE1-004	03/17/03	03/17/03	03/17/03
50-784/SE1-004 (BM)	05/08/03	05/08/03	05/08/03
50-784/SE1-004 (BI)	08/25/03	08/25/03	08/25/03
50-784/SLR-006	10/24/03	10/24/03	10/24/03
50-784/SLR-005	10/24/03	10/24/05	10/24/05

**NAME & ADDRESS OF APPLICANT:**

Pfizer Inc.  
235 East 42<sup>nd</sup> Street,  
New York, NY 10017  
Tel: (212) 573-3414  
Fax: (212) 857-3558

**CONTACT PERSONS:**

Rita Wittich  
Vice President,  
Worldwide Regulatory Strategy  
Tel: (212) 573-7271  
Fax: (212) 857-3558

**SUBMISSION REVIEWED:**

Adults: Azithromycin treatment for acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. Drug Regimen: 500 mg once daily for three days in adults.

In addition, the applicant proposes:

Children: Azithromycin treatment for acute bacterial sinusitis (ABS) caused by *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. Drug Regimen: 10 mg/ kg for three days in children six months and older.

**DRUG PRODUCT NAME:**

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

**DOSAGE FORM:** Film-coated modified capsular shaped tablet.

**POTENCY:** 500 mg azithromycin (as azithromycin dihydrate) / tablet

**ROUTE OF ADMINISTRATION:** Oral

**DISPENSED:**  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, 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  
NDA 50-784, 500 mg film-coated tablets to treat acute bacterial exacerbations of chronic obstructive pulmonary disease (AECB) in adults, Approved 05/24/02

**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*.
- Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.
- Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid).

**CHILDREN (Pediatric Patients)**

- Acute Otitis Media (AOM) caused by *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

**REMARKS/COMMENTS:**

The Applicant submitted Supplementary (s) NDA 50-784 containing clinical and bacteriological data in support of their proposed indication *Acute Bacterial Sinusitis (ABS)* due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* in adults and children. The Clinical Microbiology Reviewer will focus on the 3-forementioned targeted microorganisms.

Much of the information is found in the original NDA 50-784, approved 11/01/91 and subsequent approved amendments and supplements. Also, refer to Clinical Microbiology Review #1 completed 05/20/02. Therefore, new microbiology data are discussed in detail, other clinical and non-targeted organisms are mentioned, and most previous submitted information omitted.

Two pivotal studies are submitted:

1. Final Study Report: Azithromycin Protocol A0661057: "A multicenter open label trial evaluating oral therapy with ZITHROMAX® (azithromycin) 500 mg/day for 3 days (1.5 grams), and 500 mg/day for 6 days (3.0 grams) for the treatment of acute bacterial sinusitis." There are Clinical and microbiological assessments in this study.
2. Final Study Report: Azithromycin Protocol A0661036: "A randomized, double-blind, multicenter trial comparing oral therapy with ZITHROMAX® (azithromycin) 500 mg/day for 3 days (1.5 grams), ZITHROMAX® (azithromycin) 500 mg/day for 6 days (3.0 grams) and oral AUGMENTIN® (amoxicillin/clavulanate) 500/125 mg tid for 10 days for the treatment of acute bacterial sinusitis." There are no microbiological assessments in this study.

The **MICROBIOLOGY** and **REFERENCES** portions of the Package Labeling for sNDA 50-784/SE1-004 follows the previously approved NDA 50-784 labeling for the 500 mg film-coated tablets, approved May 24, 2002. NDA 50-710 and NDA 50-711 are referenced for updated labeling.

**Explanation on the aforementioned Submission/Types:**

NDA 50-784/SE1-004, Original Supplement, dated 03/17/03  
NDA 50-784/SE1-004 (BM), Supplemental amendment, dated 05/08/03  
NDA 50-784/SE1-004 (BI), Applicant's responses to microbiology questions, dated 08/25/03  
NDA 50-784/SLR-006, Labeling supplemental amendment, dated 10/24/03  
NDA 50-784/SLR-005, Labeling supplemental amendment, dated 10/24/03

**CONCLUSIONS:**

The Clinical Microbiology Reviewer concurs with the interpretation and conclusions on the submitted microbiological data for NDA 50-784/SE1-004 on azithromycin treatment for acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

The DAIDP/HFD-520 Medical Officer concludes that the Applicant submitted *acceptable* clinical data to support the *approval* recommendation of ZITHROMAX (azithromycin as azithromycin dihydrate) 500 mg Tablets for the treatment of acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae* in adults and children. The approved Drug Regimens are as follows: (1) Adults: 500 mg once daily for three days and (2) Children: 10 mg/ kg for three days in children six months and older, respectively.

**Package Insert Labeling:**

The **DESCRIPTION** section, **MICROBIOLOGY** section and **REFERENCES** section of the Package Labeling for NDA 50-784/SE1-004 all follow the previously approved NDA 50-784 labeling for the 500 mg film-coated tablets, approved May 24, 2002. However, the **REFERENCES** section is outdated and made current. See pages 39 to 43.

**CLINICAL MICROBIOLOGY**

**Acute Bacterial Sinusitis (ABS) Study Protocol A0661057:**

*A Multicenter Open Label Trial Evaluating Oral Therapy with Zithromax® (Azithromycin) 500 mg/day for 3 days (1.5 grams), and 500 mg/day for 6 days (3.0 grams) for the Treatment of Acute Bacterial Sinusitis.*

The central laboratory facilities, pathogen identification, and susceptibility testing procedures are acceptable. The Applicant is using NCCLS procedures and FDA/NCCLS breakpoints (NCCLS M100-S13 [M7-6/M2-A8] Supplemental Tables, dated January 2003.) [See Table 2]

**Primary Efficacy Parameter:** The primary measure of efficacy is the Applicant's assessment of bacteriological response at the EOS Visit (Visit 4, Day 28 ± 4) for the bacteriological MITT population.

**Clinical Microbiology Reviewer's Efficacy Comments:**

The clinical responses (EOS, % Cure) by baseline pathogen for the bacteriological MITT subjects are higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.9%) vs. 15/19 (78.9%). For *Haemophilus influenzae* the clinical responses (EOS, % Cure) by baseline pathogen for the bacteriological MITT subjects are lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low. [See Table 4]

The overall bacteriological responses (EOS, Visit 4, % Success) for the MITT population are almost identical for the Azith 3-Day and Azith 6-Day regimens. [See Table 5]

The bacteriological responses (EOS, % Success) by baseline pathogen for the bacteriological MITT population are higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.9%) vs. 15/19 (78.9%). For *Haemophilus influenzae* it was lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low. [See Table 6]

The success rates at EOS (EOS, % Success) by baseline pathogen for the bacteriological evaluable population is higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 32/40 (80.0%) and *Moraxella catarrhalis*, 12/13 (92.3%) vs. 13/17 (76.5%). For *Haemophilus influenzae* isolates it is lower: 23/30 (76.7%) vs. 20/24 (83.3%). *Staphylococcus aureus* is the same for both regimens: 1/1 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low. [See Table 7]

For subjects with baseline isolates, the bacteriological success rates are high (azith 3-day: 87% to 93% at EOT and 73% to 100% at EOS; azith 6-day: 93% to 100% at EOT and 77% to 100% at EOS) irrespective of the pathogen. The bacteriological success rates in subjects with *Haemophilus influenzae* are slightly higher when azithromycin is administered for 6 days.

One hundred sixty-six subjects (74 azith 3-day; 92 azith 6-day) are included in the bacteriological MITT analyses. For the bacteriological evaluable analysis, 159 subjects (71 azith 3-day; 88 azith 6-day) are included in the EOT analysis and 152 subjects (68 azith 3-day; 84 azith 6-day) are included in the EOS analysis. Similar to the clinical MITT and clinical evaluable analyses, the results from the bacteriological MITT and bacteriological evaluable analyses demonstrate that the overall bacteriological success rates are similar whether azithromycin is administered over 3 or 6 days.

Clinical Microbiology Reviewer's Conclusions:

The Clinical Microbiology Reviewer concurs with the interpretation and conclusions on the submitted microbiological data for NDA 50-784/SE1-004 on azithromycin treatment for acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

The bacteriological results for *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* isolates are *acceptable* for treatment of acute bacterial sinusitis (ABS) for 3-days using azithromycin. Overall, the bacteriological results are higher for *Streptococcus pneumoniae* and *Moraxella catarrhalis* using the 3-Day azithromycin regimen. The 6-Day azithromycin regimen gives higher bacteriological results against *Haemophilus influenzae* isolates. Therefore, the bacteriological results using the 3-Day azithromycin regimen are *acceptable*. The numbers of *Staphylococcus aureus* isolates are too few to make any definitive comment.

## EXECUTIVE SUMMARY

NDA 50-784/SE1-004  
Pfizer, Inc.

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

#### Introduction

The Applicant submitted NDA 50-784/SE1-004 for the proposed azithromycin treatment for:

(1) Adults: Azithromycin treatment for acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. Drug Regimen: 500 mg once daily for three days in adults, and

(2) Children: Azithromycin treatment for acute bacterial sinusitis (ABS) caused by *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. Drug Regimen: 10 mg/kg for three days in children six months and older, respectively.

#### 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.

An intriguing *in vitro* finding is recently reported [1]. Studies of the 50S ribosomal assembly have indicated in the past that erythromycin can inhibit assembly at concentrations higher than those required for protein synthesis inhibition. In a new study, it is found that azithromycin is much more effective (IC<sub>50</sub> 0.9 µg/mL vs. 8 µg/mL for erythromycin) at inhibiting 50S assembly. These results suggest that azithromycin binds to both mature 50S particles and the assembly intermediate equally well, and therefore may inhibit protein synthesis and ribosome assembly with equal effectiveness. It may have a dual effect on inhibiting protein synthesis.

### Intracellular Activity

Azithromycin demonstrates superiority intracellular activity against *Legionella pneumophila* in macrophages as compared with erythromycin [2].

### 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, therefore 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. The increase of macrolide resistance in pneumococci in the USA is primarily due to dissemination of strains harboring *Mef(A)*.

The distribution of *erm(B)* and *mef(A)* varies geographically. In Europe, the macrolide-resistant *Streptococcus pneumoniae* are primarily associated with *erm(B)*. In contrast, *mef(A)* is found in over two thirds of the macrolide-resistant *Streptococcus pneumoniae* in the USA. A study in Japan reports that approximately 60% of erythromycin-resistant pediatric *Streptococcus pneumoniae* isolates had the *erm(B)* gene, while 40% had the *mef(A)* gene.

Macrolide resistance in *Staphylococcus aureus* and coagulase-negative staphylococci isolated from French hospitals is 88% due to *erm(A)* or *erm(C)* genes [3]. However, there is an increase of isolates acquiring *msr(A)*, an ATP-dependent efflux pump that recognizes 14- and 15-membered macrolides and streptogramin B [4]. From 24 European university hospitals, 13% of the MSSA isolates harbored *msr(A)*. Generally, more coagulase-negative staphylococci harbor *msr(A)* than isolates of *Staphylococcus aureus* [5,6].

Efflux is mediated by either a pump with narrow specificity, such as: *Mef(A)*, *Msr(A)*, or a pump with broad specificity, such as: *AcrAB-TolC*, *MexAB-OprM*, *AmrAB-OprA*, *MtrCDE*, *MdfA*, *Cmr*. The *AcrAB-TolC* pump, or at least one homolog 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.

## CLINICAL MICROBIOLOGY

### Acute Bacterial Sinusitis (ABS) Study Protocol A0661057:

*A Multicenter Open Label Trial Evaluating Oral Therapy with Zithromax® (Azithromycin) 500 mg/day for 3 days (1.5 grams), and 500 mg/day for 6 days (3.0 grams) for the Treatment of Acute Bacterial Sinusitis.*

The central laboratory facilities, pathogen identification, and susceptibility testing procedures are acceptable. The Applicant is using NCCLS procedures and FDA/NCCLS breakpoints (NCCLS M100-S13 [M7-6/M2-A8] Supplemental Tables, dated January 2003.) [See Table 2]

Primary Efficacy Parameter: The primary measure of efficacy was the sponsor's assessment of bacteriological response at the EOS Visit (Visit 4, Day 28 ± 4) for the bacteriological MITT population.

Clinical Microbiology Reviewer's Efficacy Comments:

The clinical responses (EOS, % Cure) by baseline pathogen for the bacteriological MITT subjects are higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.9%) vs. 15/19 (78.9%). For *Haemophilus influenzae* it was lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are few. [See Table 4]

The overall bacteriological responses (EOS, Visit 4, % Success) for the MITT population are almost identical for the Azith 3-Day and Azith 6-Day regimens. [See Table 5]

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For subjects with baseline isolates, the bacteriological success rates are high (azith 3-day: 87% to 93% at EOT and 73% to 100% at EOS; azith 6-day: 93% to 100% at EOT and 77% to 100% at EOS) irrespective of the pathogen. The bacteriological success rates in subjects with *Haemophilus influenzae* are slightly higher when azithromycin is administered for 6 days.

One hundred sixty-six subjects (74 azith 3-day; 92 azith 6-day) are included in the bacteriological MITT analyses. For the bacteriological evaluable analysis, 159 subjects (71 azith 3-day; 88 azith 6-day) are included in the EOT analysis and 152 subjects (68 azith 3-day; 84 azith 6-day) are included in the EOS analysis. Similar to the clinical MITT and clinical evaluable analyses, the results from the bacteriological MITT and bacteriological evaluable analyses demonstrated that the overall bacteriological success rates are close whether azithromycin is administered over 3 or 6 days.

Clinical Microbiology Reviewer's Conclusions:

The Clinical Microbiology Reviewer concurs with the interpretation and conclusions on the submitted microbiological data for NDA 50-784/SE1-004 on azithromycin treatment for acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

The bacteriological results for *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and

*Haemophilus influenzae* isolates are *acceptable* for treatment of acute bacterial sinusitis (ABS) for 3-Days using azithromycin. Overall, the bacteriological results are higher for *Streptococcus pneumoniae* and *Moraxella catarrhalis* using the 3-Day azithromycin regimen. The 6-Day azithromycin regimen gives higher bacteriological results against *Haemophilus influenzae* isolates. However, the bacteriological results using the 3-Day azithromycin regimen are *acceptable*. The numbers of *Staphylococcus aureus* isolates are too few to make any definitive comment.

## BIBLIOGRAPHY

- <sup>1</sup> Champney, W. S. and M. Miller. 2002. Inhibition of 50S ribosomal subunit assembly in *Haemophilus influenzae* cells by azithromycin and erythromycin. *Curr Microbiol* 44:418-424.
- <sup>2</sup> Lina, G., A. Quaglia, M. E. Reverdy, R. Leclercq, F. Vandenesch, and J. Etienne. 1999. Distribution of genes encoding resistance to macrolides, lincosamides, and streptogramins among staphylococci. *Antimicrob Agents Chemother.* 43:1062-6.
- <sup>3</sup> Schmitz, F. J., R. Sadurski, A. Kray, M. Boos, R. Geisel, K. Kohrer, J. Verhoef, and A. C. Fluit. 2000. Prevalence of macrolide-resistance genes in *Staphylococcus aureus* and *Enterococcus faecium* isolates from 24 European university hospitals. *J Antimicrob Chemother.* 45:891-4.
- <sup>4</sup> Jenssen, W. D., S. Thakker-Varia, D. T. Dubin, and M. P. Weinstein. 1987. Prevalence of macrolides-lincosamides-streptogramin B resistance and *erm* gene classes among clinical strains of staphylococci and streptococci. *Antimicrob Agents Chemother.* 31:883-8.
- <sup>5</sup> Eady, E. A., J. I. Ross, J. L. Tipper, C. E. Walters, J. H. Cove, and W. C. Noble. 1993. Distribution of genes encoding erythromycin ribosomal methylases and an erythromycin efflux pump in epidemiologically distinct groups of staphylococci. *J Antimicrob Chemother.* 31:211-7.
- <sup>6</sup> Edelstein, P. H. 1995. Review of azithromycin activity against *Legionella* spp. *Pathologie Biologie* 43:569-72.

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Azithromycin is an approved drug. Much of the information is found in the original NDA 50-784, approved 11/01/91 and subsequent approved amendments and supplements (see the aforementioned **RELATED DOCUMENT(s)** section on page 1). Also, refer to Clinical Microbiology Review #1, 05/20/02 date completed. Therefore, references to previous information submitted by the Applicant are omitted.

## I. INTRODUCTION

The sNDA provides for the addition of a new indication, acute bacterial sinusitis (ABS), for adults. The Dosing Regimen is as follows: Adults: 500 mg azithromycin once daily for three days. The proposed pathogens for ABS are as follows: *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*

Sinusitis is a common infection that encompasses a spectrum of acute and chronic syndromes differentiated by the rate of recurrence and length of illness. Acute sinusitis symptoms last as long as 4 weeks [1]. Sub-acute sinusitis has minimal to moderate symptoms that are present for 4 to 12 weeks. The Applicant defines recurrent sinusitis as 4 or more episodes in one year, each episode lasting more than 7 days, with complete resolution between episodes. Chronic sinusitis persists for more than 12 weeks, often has a pathophysiology differing from acute sinusitis [2], and characterized by inflammation and eosinophilia.

Acute bacterial sinusitis is an acute infection of the paranasal sinuses and nose lasting at least 7 days and less than 4 weeks that is often preceded by a viral upper respiratory tract infection or allergic inflammation [3,4]. The causative organisms of acute bacterial sinusitis predominantly include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and less frequently, *Staphylococcus aureus* and *Streptococcus pyogenes*. Antibiotic therapy for acute bacterial sinusitis is generally empiric due to the invasive nature of obtaining culturable material from the paranasal sinuses and culture results are not routinely available for at least 48 hours following specimen submissions.

Treatment of acute bacterial sinusitis routinely includes 10-14 days of therapy with amoxicillin or amoxicillin/clavulanic acid, and other beta-lactams, administered 2 to 3 times per day. Quinolones and macrolides offer alternative treatment regimens with shorter dosing schedules. However, some experts recommend restricting the use of quinolones for specific infections rather than as a routinely used empiric antibiotic therapy due to an overly broad spectrum of activity and increasing rates of resistance [5,6,7].

Azithromycin is an azalide antibiotic that is structurally related to erythromycin. The long terminal half-life enables a once daily administration and a notably shorter course of treatment. The pharmacokinetic characteristic profile of azithromycin is extensive tissue distribution and phagocytic delivery to inflamed tissues. Here are reports in patients with acute sinusitis, azithromycin, 500 mg, achieves therapeutic concentrations in sinus fluid and mucosa persisting at significant levels for up to four days after administration. Possible higher concentrations of azithromycin in sinus fluids appear in an acute inflammatory condition perhaps as a result of phagocyte delivery of antibiotic to inflamed areas [8].

Three and 6 day dosing regimens of azithromycin are studied to determine the optimal dosing schedule and explore flexible schedules, as indicated for the use of other antimicrobials for acute bacterial sinusitis (i.e., levofloxacin for 10 to 14 days).

## II. PRECLINICAL EFFICACY (*IN VITRO*)

### A. Mechanism(s) 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. No new information is submitted by the Applicant.

Finally, an intriguing *in vitro* finding was recently reported [9]. Studies of the 50S ribosomal assembly have indicated in the past that erythromycin can inhibit assembly at concentrations higher than those required for protein synthesis inhibition. In a new study, it is found that azithromycin is much more effective ( $IC_{50}$  0.9  $\mu\text{g/mL}$  vs. 8  $\mu\text{g/mL}$  for erythromycin) at inhibiting 50S assembly. These results suggest that azithromycin binds to both mature 50S particles and the assembly intermediate equally well, and therefore may inhibit protein synthesis and ribosome assembly with equal effectiveness. It may therefore have a dual effect on inhibiting protein synthesis.

### B. Antimicrobial Spectrum of Activity

The most recent set of guidelines issued in January 2002 [10] are used in the data assessment for *Streptococcus pneumoniae* and *Haemophilus influenzae* in this sNDA.

### C. *In Vitro* Antimicrobial Activity

The Applicant proposes the following claim in this supplement: Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. Therefore, the emphasis for discussion will be on the 3-mentioned microorganisms.

The most recently published data on susceptibility to key pathogens are reviewed below. These data draw from a number of key studies, and the information is summarized.

#### *Streptococcus pneumoniae*

Recent analysis of worldwide results from the PROTEKT study (1999-2000) show 31% of *Streptococcus pneumoniae* isolates in this survey are resistant to macrolides. Overall, resistance rates varied, depending on the geographic area where the study is performed. In the US, 31% of *Streptococcus pneumoniae* strains are resistant to azithromycin. Asian countries have the highest rates of macrolide resistance, averaging 80%, while the rate of macrolide resistance for the rest of the world ranges from 11.6 to 29.1% [11].

The distribution of mechanisms of resistance is determined for 1043 macrolide-resistant *Streptococcus pneumoniae* isolates from the PROTEKT 1999-2000 study and are as follows: 35.3% *mef(A)*, 56.2% *erm(B)*, 6.8% both *mef(A)* and *erm(B)*, 0.2% *erm(A)* subclass *erm(TR)* and 1.5% negative for mechanisms tested. Mechanisms of resistance varied widely between countries and geographic regions with *mef(A)* predominating in North America and *erm(B)* in Europe [12].

PROTEKT US was initiated in 2000 to monitor resistant phenotypes and genotypes of the major respiratory pathogens across the US. For the 2000/2001 respiratory season the distribution of macrolide resistance mechanisms for 3,053 macrolide resistant *Streptococcus pneumoniae* isolates collected from outpatients with RTIs is 70.7% *mef(A)*, 17.3% *erm(B)*, 9.8% both mechanisms, 0.1% *erm(TR)* and for 2% no mechanism detected [13]. The proportion of macrolide resistance due to *mef(A)* in the US remains constant at approximately 30% since 1997 [14].

The rates of macrolide resistance reported for over 14,000 *Streptococcus pneumoniae* isolates from the TeqCES Study (1999-2000), and the TRUST Program (1999-2000) are 25.3%, and 26.6%, respectively. The rate of clindamycin resistance in these studies ranged from 4.7 to 7.2% [15].

The European Antimicrobial Resistance Surveillance System (EARSS) is an international network of 600 laboratories in 27 countries which collects comparable and validated antimicrobial susceptibility data for selected pathogens including *Streptococcus pneumoniae*. From 1999 to 2001, nearly 12,000 *Streptococcus pneumoniae* isolates are tested for erythromycin susceptibility. The overall rate of macrolide resistance is 17.6%. The highest rates of macrolide resistance are found in Italy, France and Belgium (> 30%), while the lowest rates of macrolide resistance are found in the Czech Republic (< 3%), followed by the Scandinavian countries, the Netherlands, Germany, Austria and Iceland (3 to 10%) [16]. In most countries macrolide resistance is more prevalent among penicillin intermediate and resistant *Streptococcus pneumoniae* isolates [17].

An MIC<sub>90</sub> ≥ 8 µg/mL is observed for 3 macrolides (erythromycin, clarithromycin and azithromycin) in a 1999 to 2000 surveillance study of 1,531 pneumococcal isolates. The overall rate of macrolide resistance is 26%. Of the penicillin-resistant *Streptococcus pneumoniae* isolates, 76 to 78% are resistant to the macrolides (clarithromycin, erythromycin, azithromycin) while 43% of penicillin-intermediate strains are macrolide resistant [14]. According to a recent surveillance report of 2,245 respiratory isolates of *Streptococcus pneumoniae*, macrolide resistance in Canada is approximately one-third (11%) of that seen in the USA [18].

Several publications appeared that compare *Streptococcus pneumoniae* resistance rates to clinical cure rates obtained with azithromycin or clarithromycin therapy [19,20]. Both studies suggest the resistance seen in surveillance studies is not borne out by clinical failure rates for these two macrolides. There are recent discussions regarding whether azithromycin and clarithromycin could cover the *Streptococcus pneumoniae* and *Streptococcus pyogenes* strains harboring *mef(A)*, a resistance determinant that mediates efflux of 14- and 15-membered macrolides [20,21]. Many of these strains have MICs ≤ 8 µg/mL to azithromycin. The accumulation of drug in inflammatory cells and transport of azithromycin to the site of infection may explain why the correlation between *in vitro* susceptibility testing and clinical outcome in *mefA* infections may not be strong. For example, in a prior Sponsor study on the single dose regimen of azithromycin for acute otitis media (AOM) treatment, 7 of 8 patients with *mefA* *Streptococcus pneumoniae* are clinically cured. There are some suggestions of reduced virulence for highly resistant strains [22].

In summary, the frequency of *Streptococcus pneumoniae* resistant to azithromycin in the USA increased since the original application.

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### *Haemophilus influenzae*

The frequency of resistant *Haemophilus influenzae* strains decreased from 4% to  $\leq 0.2\%$ . This decrease probably reflects better standardization of laboratory methods and a change in the MIC and agar diffusion susceptibility breakpoints from 2 to 4  $\mu\text{g/mL}$  and from  $\geq 18$  mm to  $\geq 12$  mm, respectively, according to NCCLS guidelines [10].

A 2000 to 2001 *Haemophilus influenzae* surveillance study of 1,434 respiratory isolates from the US showed that 99.7% are susceptible to azithromycin with an  $\text{MIC}_{90} = 2 \mu\text{g/mL}$  [23]. Another large worldwide surveillance study reports the same [24]. A similar surveillance study with recent United States isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* shows 99.8% and 100% of isolates susceptible to azithromycin, respectively [25]. The azithromycin  $\text{MIC}_{90}$  for *Haemophilus influenzae* is 2  $\mu\text{g/mL}$  compared with 16  $\mu\text{g/mL}$  for clarithromycin. Another US study reports 99.7% of 1,032 *Haemophilus influenzae* strains susceptible to azithromycin ( $\text{MIC}_{90} = 2 \mu\text{g/mL}$ ) [26]. *Haemophilus influenzae* harbor intrinsic efflux pumps homologous to the *acrAB-toIc* tripartite system seen in many Gram-negative bacteria [27], but no acquired resistance mechanisms to macrolides are found in this species.

### *Staphylococcus aureus*

With regard to *Staphylococcus aureus*, a recent surveillance program in hospitals in the United Kingdom shows 14.3% to 25.6% of isolates are resistant to erythromycin [28]. A study evaluated *Staphylococcus aureus* isolates collected from 15 German university hospitals from 1996 to 1999 found 19.1% of the isolates are macrolide resistant, with the bulk of resistance attributable to *erm* methylases [29]. Another large European study evaluates *Staphylococcus aureus* (April 1997 to December 1998) found macrolide resistance due to efflux (*msr(A)*) is only found in MSSA isolates, the *erm(C)* methylase is more prevalent in MSSA, whereas the *erm(A)* is more prevalent in MRSA [30]. US isolates collected in 1997 from patients with blood stream infections show 53.5% and 95.4% of the MRSA and MSSA, respectively, are erythromycin resistant [31]. Erythromycin resistance in bloodstream isolates collected during the first six months of 1998 in the US reveals 31.4% and 93.1% for MSSA and MRSA. For coagulase-negative staphylococci, the frequency of erythromycin resistance is 50.8% and 87.4% in oxacillin susceptible and oxacillin-resistant US isolates in 1997 and 31% and 76% in 1998 [31,32]. *Streptococcus aureus* isolates from patients with skin and soft tissue infections collected from 30 US hospitals and 8 Canadian medical centers in 1997 are 49.4% erythromycin resistant [33]. No studies are done recently to discern the macrolide resistance mechanisms in staphylococcal isolates in the US, but an older study reveals that *erm(A)* or *erm(C)* accounted for the majority of resistance [34].

### *Moraxella catarrhalis*

A study of the epidemiology of sinusitis (RESP) from the 1999 to 2000 season found the most commonly observed pathogens are *Moraxella catarrhalis* (28.9%), *Haemophilus influenzae* (21.7%), *Staphylococcus aureus* (17.9%), PenS *Staphylococcus pneumoniae* (7.2%) and Pen IR *Streptococcus pneumoniae* (4.0%) [35]. Both *Moraxella* and *Haemophilus* spp. are highly susceptible ( $> 99\%$ ) to azithromycin. Pneumococci are 64% susceptible, and staphylococci 31% susceptible, with an additional 18.7% intermediate. In a similar vein, an antimicrobial surveillance study (PROTEKT) of *Haemophilus influenzae* and *Moraxella catarrhalis* from community respiratory infections found 99.8% of *Haemophilus influenzae* and 100% of *Moraxella catarrhalis* susceptible to azithromycin by established MIC cutoff values [36].

Another surveillance study with recent United States isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* shows 99.8% and 100% of isolates susceptible to azithromycin, respectively [25].

A recent review of the treatment of sinusitis in children reviewed several therapeutic modalities [37]. The study concluded that newer macrolides are as effective as amoxicillin, and azithromycin, with a shorter course of therapy, may offer compliance advantages. Another study found in cases where bacteria are present in nasal secretions, they might play a pathogenic role in upper respiratory infections [38]. This study centered on the use of azithromycin, and in cases where *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis* are present as determined by culture, azithromycin reduced duration of symptoms and complications.

#### D. Mechanisms of Resistance Studies

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, therefore 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. The increase of macrolide resistance in pneumococci in the USA is primarily due to dissemination of strains harboring this determinant.

The distribution of *erm(B)* and *mef(A)* varies geographically. In many countries in Europe, the macrolide-resistant *Streptococcus pneumoniae* are primarily associated with *erm(B)*. In contrast, *mef(A)* is found in over two thirds of the macrolide-resistant *Streptococcus pneumoniae* in the USA. A study in Japan reports that approximately 60% of erythromycin-resistant pediatric *Streptococcus pneumoniae* isolates had the *erm(B)* gene, while 40% had the *mef(A)* gene.

Macrolide resistance in *Staphylococcus aureus* and coagulase-negative staphylococci isolated from French hospitals is 88% due to *erm(A)* or *erm(C)* genes [39]. However, there are an increase of isolates acquiring *msr(A)*, an ATP-dependent efflux pump that recognizes 14- and 15-membered macrolides and streptogramin B [30,39]. From 24 European university hospitals, 13% of the MSSA isolates harbored *msr(A)*. Generally, more coagulase-negative staphylococci harbor *msr(A)* than isolates of *Staphylococcus aureus* [34,40].

Efflux is mediated by either a pump with narrow specificity, such as: *Mef(A)*, *Msr(A)*, or a pump with broad specificity, such as: *AcrAB-TolC*, *MexAB-OprM*, *AmrAB-OprA*, *MtrCDE*, *MdfA*, *Cmr*. The *AcrAB-TolC* pump, or at least one homolog 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.

#### E. Miscellaneous - Experimental Studies

##### *Streptococcus pneumoniae*

There are conflicting reports on the effect of azithromycin on nasopharyngeal (NP) carriage. These conflicts may arise as a result of the differences in study designs; some studies measure the impact of antibiotic treatment within 3-4 days of initiation of treatment [41] compared 2 weeks or ≥ one month after antibiotic treatment [42,43,44,45]. There are no studies in which seasonal changes in NP carriage is taken into account nor are these studies controlled by assessing carriage in an untreated population over time. Also, an initial higher prevalence of antibiotic-

resistant NP flora in a specific geographical area impact transmission and subsequent NP colonization. Given all these limitations, the studies do emerge with one common theme - antibiotics have selective effects, killing susceptible, and in some cases, a certain percentage of non-susceptible microorganisms. The greatest impact on the NP carriage is seen during or shortly after drug treatment [42-45,46]. For example, in patients treated with amoxicillin/clavulanate, carriage of *Streptococcus pneumoniae* significantly decreased [44]. The authors conclude that a greater percentage of the remaining pneumococci are resistant, but there is no way to assess if the resistant strains are resident before drug treatment or obtained by exposure to a carrier of penicillin-resistant pneumococci.

The reduction in carriage of *Streptococcus pneumoniae* is seen in a number of studies and for multiple antibiotics, including azithromycin. In a recent study designed to evaluate the efficacy of azithromycin for eradication of oropharyngeal Group A streptococci as well as its impact on the NP colonization rate of *Streptococcus pneumoniae*, [46] NP colonization rates for pneumococci decreased from 46% to 12% by day 17 and are 20% by day 32. The prevalence of azithromycin-resistant isolates increase from 2% to 4% by day 17 and to 8% by day 32. Analyses by serotyping, genotyping, and antimicrobial susceptibility provided no evidence that any individual strain present before therapy is resistant or present and previously missed. Therefore, it is likely that antibiotic-resistant strains are acquired by contact with other carriers. Consistent with this, the majority of studies that evaluate the resistant or persistent strains after antibiotic therapy usually find a small proportion of the pneumococci to be clonally related to the initial isolate.

One recent study found that the carriage of non-pneumococcal alpha-hemolytic streptococci increased after either amoxicillin/clavulanate or azithromycin treatment [43]. However, there are no data to show that the alpha-hemolytic streptococci are present before therapy became resistant after therapy. Interestingly, the more highly resistant pneumococcal strains do not appear to account for any greater proportion of acute otitis media illness despite seasonal fluctuations of NP carriage [47].

More exploration on the different populations that constitute the NP flora needed to adequately interpret the impact of antibiotic usage. The alteration of NP flora permit habitation of new organisms or provide a reservoir of non-pneumococcal alpha-hemolytic streptococci that are antibiotic resistant.

### ***Haemophilus influenzae***

As regards *Haemophilus influenzae* carriage, the impact of either  $\beta$ -lactam or azalide treatment is less profound [44]. Azithromycin used for community treatment of children with trachoma shows to have no effect on increasing the incidence of *Streptococcus pneumoniae* resistance to azithromycin in NP cultures [48] or in conjunctival bacterial flora [49]. Azithromycin administration, as compared to clarithromycin administration, for both *Mycobacterium avium* prophylaxis or therapy, shows to lead to less break-through of resistance in *Mycobacterium avium* isolates [50,51].

## **F. Post-Antibiotic and Post-Antibiotic Sub-MIC Effects**

### **Post-antibiotic effect (PAE):**

An *in vitro* PAE of 2.2 and 3.5 h is observed for azithromycin vs. *Staphylococcus aureus* and *Escherichia coli*, respectively. [52] Reports of PAEs of between 2.2 and 4.7 h are observed for *Streptococcus pneumoniae* [53,54] and *Haemophilus influenzae* [53,54,55]. One paper reported a PAE of > 12 h for a penicillin-resistant isolate of *Streptococcus pneumoniae* and a mean PAE of

2 h for *Moraxella catarrhalis* strains [56].

The PAE of 5X the MIC of azithromycin against 20 pneumococcal strains ranged from 1 to 6 h. *In vivo* azithromycin PAEs of 3.6 to 13.1 h are reported for *Staphylococcus aureus* [52,53] and 11 h for *Streptococcus pneumoniae* [53] using the neutropenic mouse thigh model. A significant decrease in the virulence of post-antibiotic-phase pneumococci is measurable by increases in LD<sub>50</sub> values [57].

The sub-MIC effect of azithromycin at 0.1X, 0.2X, or 0.3X the MIC for *Streptococcus pneumoniae* is 1.7, 6.2, or 12.0 h, respectively. The *in vivo* post-antibiotic 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 [53,57].

### III. PRECLINICAL EFFICACY (IN VIVO)

#### Pharmacokinetics and Pharmacodynamics

When a 1.5 gm total dose of azithromycin is given over 5 days or 3 days the levels in tonsils of pediatric patients are projected to exceed 2 µg/mL ten days after initiation of therapy [58,59]. The mean concentration of azithromycin in tonsillar and adenoid tissue from children at 4 and 11 days after the start of a 3-day 10 mg/kg dosage regimen is 10.33 and 1.49 µg/g, respectively [59]. These concentrations are well above the susceptibility breakpoint for streptococci, ≤ 0.5 µg/mL. Children ages 1 to 6 years with secretory otitis media receiving a 10 mg/kg dose of azithromycin prior to tympanostomy have mean azithromycin concentrations of 3.97 and 1.42 µg/mL at 24 h or 48 h post-administration [60]. The mean concentration in uninfected lung tissue 5 days after a 500 mg dose of azithromycin is 3.13 µg/g [61]; this is above the MIC<sub>90</sub> for *Haemophilus influenzae* of 2 µg/mL and susceptible streptococci (≤ 0.12 µg/mL). The mean concentration in gynecological tissue is 1.44 and 0.78 µg/g at 1 and 4 days following a 500 mg dose [62].

Laboratory experiments with azithromycin suggest it is the total amount of drug given rather than the interval of the dosing regimen that determines the concentration at the infection site and results in efficacy [53, 63, and Appendix 1, Table 1, on page 37]. Interestingly, however, the additional component of C<sub>max</sub> may also factor into the effectiveness of the regimen. In the murine intranasal lung model with a macrolide-susceptible *Streptococcus pneumoniae* challenge, azithromycin performs best administered orally as a single dose rather than given once daily for three days [Appendix 1, Pfizer in-house studies]. These data suggest Peak/MIC as well as AUC/MIC play important roles in predicting efficacy. The PD<sub>50</sub> for the one-day regimen is 20.4 mg/kg versus 49.4 mg/kg for the same dose given as a three-day regimen. In an acute murine model challenged with a macrolide-susceptible *Streptococcus pyogenes*, performance is also best when azithromycin is given as a single dose [Appendix 1, Pfizer in-house studies]. In a third model, a murine acute infection model with an *Enterococcus faecalis* challenge, efficacy with azithromycin was best as a single dose (14.8 versus 42.7 and 59.3 mg/kg for 1, 2, or 3 day regimens of the same total dose, respectively) [Appendix 1, Pfizer in-house studies]. Therefore, using the same total therapeutic dose, the duration of treatment with azithromycin is reduced and appears to be more efficacious [63, and Appendix 1, Pfizer in-house studies]. While AUC/MIC still predicts efficacy, the results reflect the contribution of additional factors, C<sub>max</sub> and azithromycin's prolonged persistent effects, on efficacy.

Because inflammatory cells provide a mode of transport and reservoir for azithromycin to the infection site, [53, 64, 65, 66, 67, 68] it seems reasonable to give large azithromycin doses as early as practical during the period of maximum inflammation associated with the infection. Administering the same total dose as a single dose or in three days instead of 5 days results in

higher concentrations in the infected tissue at early times after treatment due to increased initial dosing and increased inflammation [63, Fig. 2]. The higher initial concentration at the infection site may help prevent less susceptible sub-populations of the pathogens initially present from becoming established. This has been proposed as the reason for less *in vivo* emergence of resistance to azithromycin compared with clarithromycin in patients who received either drug for treatment or prophylaxis against *Mycobacterium avium* [50]. A shorter oral dosage regimen also results in greater patient compliance, which contributes to reduced emergence of less susceptible strains.

The efficacy of a weekly dose of azithromycin (500 mg/week) determined in a clinical study where oral prophylaxis of azithromycin is compared to benzathine penicillin G (BPG) and a no-treatment group in a military population [69]. U. S. Marine trainee volunteers evaluated for evidence of acute respiratory disease by serological testing of pre-training and post-training sera. Azithromycin outperforms BPG, preventing infection from *Streptococcus pyogenes* (84% efficacy), *Streptococcus pneumoniae* (80% efficacy), *Mycoplasma pneumoniae* (64% efficacy), and *Chlamydia pneumoniae* (58% efficacy) in comparison with results in the no-treatment group. The results in this population are all the more notable as trainees are reluctant to seek relief in the infirmary, true to their stoic military training. According to serological tests, oral azithromycin is found to be an effective alternative prophylaxis to BPG for military populations.

## 1. Animal Model Studies

For intracellular pathogens, the concentration of drug in the infected macrophages is important. Infected macrophages take up more drug than non-infected cells [65]. The concentration of azithromycin in the bronchoalveolar lavage from guinea pigs infected with *Legionella pneumophila* is significantly higher than the bronchoalveolar lavage from non-infected animals. This helps explain the superior potency of azithromycin as compared to other macrolides in the *Legionella pneumophila* guinea pig infection model [65]. Therefore, the phagocytes, in their natural process of fighting an infection, take up, transport and release azithromycin at the site of infection. Other macrolides and  $\beta$ -lactams do not show significantly high sustained concentrations at the infection site [63, 67, 70, 71]. In contrast to azithromycin, their concentrations are reduced in the early *Staphylococcus aureus* abscess model [63].

The phagocyte delivery mechanism is fully operational even when circulating granulocytes are reduced 70 to 85% by cyclophosphamide treatment in a *Staphylococcus aureus* mouse thigh model [72]. In this study, equivalent efficacy is observed in leukopenic mice compared with normal mice (Fig. 5, Reference [72]) Under conditions of severe neutropenia, higher levels of azithromycin are not observed in infected versus healthy lung tissue in a *Streptococcus pneumoniae* lung infection model [67]. Surprisingly, serum levels in cyclophosphamide-treated uninfected animals are less than one-fourth that of normal animals and lung tissue concentrations are less than one-half that of normal animals. Therefore, there are major differences in these models relative to the degree of neutropenia and its impact on the available phagocyte population and cyclophosphamide toxicity. [See discussion section of Reference 72.]

## 2. Human Studies:

Study A0661057 provides pivotal clinical and bacteriological evidence for the use of azithromycin for sinusitis. Microorganisms most commonly isolated as agents involved with sinusitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus*. Of these organisms, changes in susceptibility to *Streptococcus pneumoniae* are most likely changed since the introduction of this product over ten years ago. Many pneumococci have acquired *mef* or *erm* determinants conferring resistance in this species. Despite MICs out of the

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range of susceptible, many pneumococci are reported to be eradicated in respiratory infections. This is likely due to the high tissue distribution of azithromycin and its ability to concentrate in white blood cells.

A review of the organisms collected at baseline in Study Protocol #A0661057 indicates that the majority are susceptible to azithromycin.

The following section describes the susceptibility of four species of organisms collected in this study and the bacteriological and some clinical outcomes of the subjects infected by these organisms.

#### IV. CLINICAL EFFICACY and CLINICAL MICROBIOLOGY

##### (Acute Bacterial Sinusitis Study Protocol #A0661057)

###### General Information:

Protocol Study #A0661057 provides pivotal clinical and bacteriological evidence for the use of azithromycin for sinusitis. Microorganisms most commonly isolated as agents involved with sinusitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus*. The first 3-microorganisms are the proposed targeted microorganisms in this submission and are discussed in this Clinical Microbiology Review. Of these organisms, changes in susceptibility to *Streptococcus pneumoniae* changed since the introduction of this product over ten years ago. Pneumococci acquired *mef* or *erm* determinants conferring resistance in this species. Despite MICs out of the range of susceptible, many pneumococci are reported to be eradicated in respiratory infections. This is likely due to the high tissue distribution of azithromycin and its ability to concentrate in white blood cells.

###### Protocol Study: A0661057

Protocol Study Title: *A Multicenter Open Label Trial Evaluating Oral Therapy with Zithromax® (Azithromycin) 500 mg/day for 3 days (1.5 grams), and 500 mg/day for 6 days (3.0 grams) for the Treatment of Acute Bacterial Sinusitis.*

Study Dates: April 24, 2001 to August 13, 2002

Report Date: December 30, 2002

Country Study Sites: United States, Latin America (Argentina, Chile, Costa Rica, Guatemala, Mexico, and Panama), and Finland.

Fifty-five Study Sites: 38 US; 12 Latin America (Argentina = 3, Chile = 1, Costa Rica = 3, Guatemala = 1, Mexico = 3, Panama = 1) and 5 Finland.

Study Design: This is a multicenter, open-label, randomized study.

###### Study Objectives:

The primary objective of this study is to evaluate the bacteriologic efficacy of oral Zithromax® (azithromycin) administered as 500 mg day for 3 days versus 500 mg/day for 6 days in the treatment of subjects with acute bacterial sinusitis (ABS).

The secondary objectives are to compare the clinical efficacy and safety and toleration of Zithromax<sup>®</sup> (azithromycin) dosed as 500 mg/day for 3 days versus 500 mg/day for 6 days.

Age/Gender: Subjects of either gender, 18 years of age and older who meet rigorous clinical and radiological entrance criteria for acute bacterial infection of the maxillary sinuses are eligible for entry into this study.

Clinical and Microbiological Inclusion/Exclusion Criteria:

Subjects are enrolled in the study after satisfying the inclusion/exclusion criteria, including provision of the appropriate informed consent. At Baseline, all subjects have a targeted physical examination, clinical laboratory assessments, a sinus transantral puncture (TAP) and aspiration, and provided a medical history. A sinus radiograph is obtained at the baseline visit, unless one is performed within the previous 48 hours.

Sinus radiographs (Waters' view – Caldwell's and lateral views only if Waters' is inconclusive) are obtained and read by qualified radiologists locally.

- Study Population Includes:

Microbiological Inclusion Criteria

Subjects who meet the following microbiological related criteria are considered for enrollment into the study and could receive study drug, if eligible.

1: Subjects must have clinically documented acute bacterial infection of the maxillary sinuses including one or both of the following signs and symptoms lasting longer than 7 days but less than 28 days:

- Purulent nasal discharge
- Subjects may have other diagnostic symptoms, including hyposmia, jaw pain with mastication, nasal congestion, headache, halitosis, and a history of recent upper respiratory infection.

2. Subjects who have a positive sinus X- ray (i.e., opacification of the affected sinuses, an air-fluid level, or  $\geq 6$  mm mucosal thickening).

3. Subjects willing to undergo direct aspiration of the sinus cavity.

Microbiological Exclusion Criteria

Subjects with any of the following microbiological related conditions are not enrolled in this study.

1. Subjects with an allergy, hypersensitivity, or other contraindications to any macrolide antibiotic.
2. Subjects who were currently hospitalized for any reason.
3. Subjects who were treated with any other systemic antibiotic for 24 hours or longer within 2 weeks prior to the baseline visit.

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4. Subjects with infections that may have required treatment with an antibiotic other than the study drug.
5. Subjects with a recent history of chronic sinusitis including but not limited to those subjects with three or more episodes of sinusitis in the last 6 months.
6. Subjects who have had a history of sinus surgery other than for a diagnostic procedure within a year prior to the baseline visit.
7. Subjects with significant gastrointestinal or other conditions that could affect study drug absorption.
8. Subjects with evidence or history of significant hematological, renal or cardiovascular disease or immunologic compromise (i.e., neutropenia, ARC [AIDS-related complex]/ AIDS [acquired immunodeficiency syndrome], non-skin cancers or malignant melanoma).
9. Subjects who receives any investigational drug during the previous 30 days or five times the plasma half-life (if known), whichever was longer, or who previously participated in this trial.
10. Subjects in whom concurrent use of certain medications with study drug may interfere with the evaluation of the study drug.
11. Subjects with any condition that, in the opinion of the investigator, affect subject safety, precluded evaluation of response, or make it unlikely that the contemplated course of therapy and follow-up is completed, or who were unable/ unlikely to follow the study protocol.

- Amendments:

There are two amendments to the protocol, 11 July 2001, and 18 April 2002. The amendment does not affect efficacy or safety procedures performed on those subjects enrolled in the study prior to the implementation of the amendments. The informed consent form is revised in accordance with Amendment 2 and changes are communicated to the sites through the monitoring Contract Research Organization (CRO) or the internal country offices wherever implemented.

The 1<sup>st</sup> Amendment included the following microbiology related changes:

- Inclusion of centers in Latin America (Argentina, Chile, Costa Rica, Guatemala, Panama, and Mexico) and Europe.
- Clarification of TAP culture guidelines which included the requirement of local laboratories to examine the specimen by Gram stain, quantitative aerobic culture, and identification of pathogen. Endoscopically guided cultures in the absence of sinus puncture are not acceptable.
- Inclusion of microbiological methods in *Appendix E* of the protocol.

The 2<sup>nd</sup> Amendment included the following changes to the protocol:

- Randomization is allowed to continue in only one treatment group after the required number of subjects with target pathogens had been reached in the other treatment group.
- The sample sizes increased from 300 subjects to approximately 500 subjects to ensure there are an adequate number of subjects with each of the target pathogens within each treatment group.

This is necessary because 1) the number of subjects with *Streptococcus pneumoniae* at Baseline is unevenly distributed across the two treatment groups, and 2) the number of subjects with targeted pathogens is slightly lower than anticipated.

- Sites are allowed to send the sinus aspirate directly to the central laboratory in cases where a qualified local laboratory is not available.

Investigational Drug:

Pfizer Inc. provides the study medication. All study medication is provided in bottles packed in boxes. Each bottle is to have 3 tablets. For each subject, a total of 1 or 2 labeled bottles are supplied depending on the randomization assignment at Visit 1 (Day 1). Subjects are to take the first dose of study medication irrespective of the time of day. It is recommended that this dose is taken during Visit 1. Subsequent doses are taken in the morning, preferably at the same time of day. Study medication may be taken without regard to meals.

Drug Administration: At all sites the following lot numbers and FID number are used.

- Lot Nos/FID No. N0118- G1; N0118- G2; N0118-G3/QC2468
- Dosage Form: 500 mg tablets

Dosing/Duration:

- Dosing: One 500 mg tablet per day
- Duration: Active treatment for 3 days or 6 days. Follow-up until at least 24 to 32 days.

Clinical Supplies:

All clinical supplies used in the trial are provided by the Applicant. Supplies are packaged and shipped directly from I C to all US sites. For non-US sites (Finland and Latin America), drug supplies are sent to the sites via the country offices.

Evaluation Groups:

Five hundred thirty-nine (539) subjects are randomized to azithromycin (azith) treatment (284 azith 3-day; 255 azith 6-day). Five hundred thirty-six (536) subjects (281 azith 3-day; 255 azith 6-day) are treated with study drug and are evaluable for safety analyses. Three subjects who are randomized to the azith 3-day treatment group did not receive study treatment and are not included in the efficacy and safety analyses. Of the 536 treated subjects, 273 subjects (97.2%) in the azith 3-day group and 249 subjects (97.6%) in the azith 6-day group completed treatment. There are more subjects enrolled in the azithromycin 3-day treatment group than in the azithromycin 6-day treatment group. This is because *Amendment 2* of the protocol allows randomization to continue in only one treatment group after the required number of subjects with target pathogens is reached in the other treatment group.

One hundred sixty-six subjects (74 azithromycin 3-day; 92 azithromycin 6-day) are included in the bacteriological MITT analyses. The study population being discussed in this clinical microbiology section is limited to bacteriological MITT subjects with baseline isolates tested at the central laboratory. Data are not included for subjects with baseline isolates that are not received by the Central Laboratory. In the section summarizing results with *Staphylococcus aureus*, the overall

MIC distribution is discussed for all baseline isolates, but the correlation with clinical outcome is limited to bacteriological MITT subjects (i.e., those with a baseline *Staphylococcus aureus* colony count of  $\geq 10^4$  CFU/mL).

**TABLE 1\*** shows the Applicant's Subjects Evaluation Group.

	Azith 3-Day N (%)	Azith 6-Day N (%)
Randomized	284	255
Treated	281	255
Completed Study	273 (97.2)	249 (97.6)
Discontinued Study	8 (2.8)	6 (2.4)
Analyzed for Efficacy		
Clinical MITT	281 (100.0)	254 (99.6)
Clinical Evaluable		
Visit 3 (EOT)	257 (91.5)	233 (91.4)
Visit 4 (EOS)	254 (90.4)	232 (90.2)
Bacteriological MITT	74 (26.3)	92 (36.1)
Bacteriological Evaluable		
Visit 3 (EOT)	71 (25.3)	88 (34.5)
Visit 4 (EOS)	68 (24.2)	84 (32.9)
Analyzed for Safety		
Adverse Events	281 (100.0)	255 (100.0)
Laboratory Data	281 (100.0)	255 (100.0)

\* Adopted from EDR NDA 50-784, EDR, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Table found on Page 6.

**Efficacy Assessments:**

**Clinical:**

- Visit 1 (Baseline)
- Visit 2 (Telephone Contact) is designated to occur on study Day 4 ± 1
- Visit 3, End of Therapy Visit (EOT), is designated to occur on study Day 7+ 2
- Visit 4, End of Study Visit (EOS), is designated to occur on study Day 28 ± 4

The primary efficacy outcome time point for the study is Visit 4, End of Study Visit (EOS)

**Bacteriologic:**

- Baseline Visit (Visit 1): The bacteriologic assessment includes: concurrent diseases, antibiotic therapy within the last 14 days, concomitant drug and non-drug treatments, and laboratory assessments. A sinus TAP, aspiration and culture are performed.

- Visit 2 (Telephone Contact) was designated to occur on study Day 4 ± 1.

Through telephone contact, the subject's response to therapy is determined as provided by the subject. Information on the use of concomitant drug and non-drug treatments are recorded.

At the discretion of the investigator, the subject is encouraged to return for an unscheduled visit if he or she reports feeling the same as at the previous visit. If the subject feels worse than at the previous visit, he or she is encouraged to return for an unscheduled visit as soon as possible. The investigator assesses the subject's response to therapy at this unscheduled visit. If necessary, study drug is discontinued and appropriate non-study antimicrobial therapy is initiated. Subjects who discontinue study drug are directed to return for final clinical assessments.

- Visit 3, End of Therapy Visit (EOT), Study Day 7+ 2, and Visit 4, End of Study Visit (EOS) Study Day 28 ± 4:

All signs and symptoms of sinusitis are identified at Baseline (Visit 1) are assessed and numerically graded as had been done previously. Concomitant drug and non-drug treatments are recorded. Study drug compliance is checked and clinical laboratory tests are performed at Visit 3. Clinical laboratory tests are performed at Visit 4 if a clinically significant abnormality was present or if the subject experiences a clinically significant adverse event.

A TAP and aspiration of the maxillary sinus and culture are strongly encouraged at Visits 3 or 4 only for those subjects who are failing to respond clinically to treatment.

The overall clinical success is defined by the Applicant as cure plus improvement at EOT (Visit 3, Day 7+ 2) and cure at EOS (Visit 4, Day 28 ± 4).

### **Microbiology**

#### **Sinus Aspiration:**

Transantral puncture and aspiration of maxillary sinuses for culture and susceptibility testing are performed at Baseline. If the subject fails to respond clinically to treatment, a repeat TAP is strongly encouraged.

Specimens for culture are aspirated through the needle after maxillary sinus puncture according to standard procedures at the site. Endoscopically guided cultures without sinus puncture are not acceptable. When free fluid is not obtained from the sinus cavity, up to 2.5 mL of normal saline (without preservative) solution may be instilled and aspirated to provide a specimen. The specimen is transported to the local laboratory for examination by Gram stain, quantitative aerobic culture and identification of pathogen. Pure culture of the isolated pathogen is then transported as rapidly as possible to the Central Laboratory for re-identification, susceptibility testing, and storage of the isolate.

#### **Central Laboratory Facilities and Pathogen Identification:**

Laboratory safety tests and microbiology (confirmation of bacterial identification and susceptibility testing) are performed by a Central Laboratory [ ] (For sites in the US and Latin America, samples are sent to [ ]  
[ ] For sites in Finland, samples are sent to [ ]

The clinical significance of any abnormal laboratory tests obtained during the study is assessed by the investigator.

Susceptibility Testing:

Routine susceptibility testing of isolates is conducted locally as appropriate. If available, results are to be recorded in the case report form. During the course of the study, the Central Laboratory performs susceptibility testing for all isolates obtained during the study. Susceptibility test results recorded by the central laboratory are used in the analyses of susceptibility.

General NCCLS guidelines for conducting MICs are followed according to the protocol in M100-S10, January 2002. All MIC panels are made and tests performed at [redacted]

Isolates from the US and Latin America are processed by the [redacted] facility in [redacted], and isolates from Finland are processed by the [redacted] facility in [redacted]

Panels are made and stored frozen at -70°C until needed. The MIC panels are configured in a microtiter plate format containing antibiotic concentrations arranged in serial two-fold microbroth dilution schemes within the predetermined testing ranges.

Subjects who did not have a pathogen isolated or if the pathogen is resistant to study medication are not discontinued from study drug provided they are improving clinically. Subjects with no baseline pathogen isolated are excluded from the bacteriological analysis.

Susceptibility Breakpoints:

Current FDA approved breakpoints for MICs and zone sizes are applied to all data, except for *Moraxella catarrhalis*, for which no established breakpoints exist. The Applicant uses proposed breakpoints and are applied, as defined in the package insert label (TABLE 2) and the original Zithromax NDA 50-670, approved Nov., 1991.

TABLE 2 shows the Applicant's MIC (µg/mL) and zone diameter (mm) susceptibility breakpoints used for the azithromycin studies.

Pathogen	Susceptible		Intermediate		Resistant	
	MIC <sup>a</sup>	Zone Diameter <sup>b</sup>	MIC <sup>a</sup>	Zone Diameter <sup>b</sup>	MIC <sup>a</sup>	Zone Diameter <sup>b</sup>
<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	c
<i>Moraxella Catarrhalis</i>	≤2	≥18	4	14-17	≥8	≤13

<sup>a</sup> Adopted from EDR NDA 50-784, EDR, 03/30/03, on Page 18.

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

The FDA and referenced NCCLS microbial susceptibility breakpoints are the same. Refer to NCCLS M100-S13 [M7-6/M2-A8] Supplemental Tables, dated January 2003.

Statistical Methods:

- Sample Size

In this multicenter trial each center is to continue to enroll subjects until at least 25 subjects with a positive bacterial culture for *Haemophilus influenzae* and at least 25 subjects with a positive bacterial culture for *Streptococcus pneumoniae* who are clinically and bacteriologically evaluable are enrolled in each study arm. Centers are also to enroll at least 15 *Moraxella catarrhalis* evaluable subjects per arm. However, the Applicant reserved the right to terminate the enrollment irrespective of the status of enrollment of *Moraxella catarrhalis* subjects. It is anticipated that a total of 300 subjects are needed to satisfy this criteria.

Statistical and Analytical Plans:

The statistical analyses performed are summarized below.

Study Populations Analyzed:

There are three analysis populations: 1) Clinical modified intent-to-treat (MITT), 2) Clinical Evaluable (CE), and 3) Safety. One and 2 are discussed.

1. The clinical modified intent-to-treat (MITT) population includes subjects who are clinically documented acute bacterial infection of the maxillary sinuses at Baseline of the protocol, and who receive at least one dose of study medication. The bacteriological MITT population is defined as a subset of subjects in the clinical MITT population with a positive baseline culture for *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Staphylococcus aureus* (when isolated in pure culture with a colony count of  $\geq 10^4$  CFU/mL).

2. The Clinical Evaluable (CE) population includes all subjects in the MITT population, unless any one or more of the following criteria applied:

a) Did not meet all inclusion and exclusion criteria, b) Received less than 80% of study medication except if failed and discontinued, c) Received more than 120% of study medication.

In addition, subjects who meet the following microbiological criteria are excluded from the clinical evaluable analyses at the relevant visit(s):

a) Received concomitant systemic antibiotic treatment for intercurrent illness prior to the evaluation point, b) Had no visit at the primary evaluation time point (EOS visit, Visit 4) unless the subject was previously designated as a treatment failure, c) Had a visit date outside the analysis visit window, d) Had an inappropriate, susceptible baseline pathogen (bacteriological evaluable subset only).

The bacteriological evaluable population is defined as a subset of subjects in the clinical evaluable population with a positive baseline culture for *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Staphylococcus aureus* when isolated in pure culture with a colony count of  $\geq 10^4$  CFU/mL).

All evaluability determinations are made on groups of clean subject data at regular intervals during the study prior to database release.

Efficacy Parameters:

Two populations, the clinical MITT and clinical evaluable populations are analyzed for efficacy in this study.

Primary Efficacy Parameter:

The primary measure of efficacy was the sponsor's assessment of bacteriological response at the EOS Visit (Visit 4, Day 28 ± 4) for the bacteriological MITT population.

Secondary Efficacy Parameters:

- Clinical response at the EOT Visit (Visit 3, Day 7+ 2)
- Clinical response at the EOS Visit (Visit 4, Day 28 ± 4)
- Bacteriological response at the EOT Visit (Visit 3, Day 7+ 2) for the bacteriological MITT and bacteriological evaluable populations and at EOS for the bacteriological evaluable population.

Clinical Response (summarized):

Clinical response is determined by the investigator at the EOT visit (Visit 3, Day 7+ 2) and the EOS visit (Visit 4, Day 28 ± 4) and is based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point.

The investigator classified the clinical presentation of the subject at the evaluation time point using the criteria listed below:

- Cure: Resolution of signs and symptoms of acute sinusitis to the level that existed prior to the occurrence of the acute illness. No worsening in the radiographic appearance of the sinuses noted (applicable to Visit 4 or where radiographic information is available). No antibiotics (other than study drug) are given.
- Improvement: Improvement but incomplete resolution of the signs and symptoms of acute sinusitis as defined above and no requirement for additional antibiotic. This is applicable at Visit 3 only.
- Failure: Persistence of one or more signs or symptoms of sinusitis or appearance of new signs or symptoms. Need for additional antimicrobials or change in antimicrobial therapy.
- Unknown: Subject response is not assessed due to missed visit or failure to record clinical outcome.

Bacteriological Response:

Bacteriological response is summarized on a by-subject and by-pathogen basis for the bacteriological MITT and bacteriological evaluable populations.

For those subjects for whom a pathogen is isolated at Baseline, bacteriological response is determined by the sponsor and evaluated at the EOT Visit (Visit 3, Day 7+ 2) and EOS Visit (Visit 4, Day 28 ± 4) as follows:

- Documented Eradication — Absence of the original baseline pathogen in a sinus puncture culture at Visit 3, Visit 4 or relevant visit.
- Presumed Eradication — Absence of repeat sinus puncture culture results, and the subject was a clinical cure at Visit 4 or a clinical improvement or cure at Visit 3.
- Documented Persistence — Presence of the original baseline pathogen in a sinus puncture culture at Visit 3, Visit 4 or relevant visit.
- Presumed Persistence — Absence of repeat sinus puncture culture and the subject was a clinical failure.
- Superinfection — Baseline pathogen( s) gone but another pathogen present in a sinus puncture culture.

By-subject bacteriological response assessment is based on the following hierarchy in the event that more than one outcome applied:

1. Documented Persistence
2. Superinfection
3. Presumed Persistence
4. Presumed Eradication
5. Documented Eradication

The by-pathogen bacteriological response assessments are similar to those described above for the by-subject bacteriological response with the exception that *Superinfection* is not included as a response category.

Efficacy Analyses:

- Bacteriological Response

Bacteriological eradication rates and 95% confidence intervals (Documented Eradication + Presumed Eradication) are displayed by treatment group for all bacteriological MITT and bacteriological evaluable populations combined as well as by baseline pathogen separately (where numbers of pathogens are sufficiently large). Results are also displayed by country.

- Baseline Susceptibility

All baseline pathogens received by the Central Laboratory are tested for susceptibility to study drug. The MIC values, categorized as susceptible, intermediate and resistant, are summarized and displayed. A tabulation of baseline susceptibility and clinical outcome are constructed by country. In addition, a correlation between susceptibility based on minimum inhibitory concentration (MIC) and zone size is presented.

- Missing Values

In the summaries of clinical response (clinical MITT and clinical evaluable populations) and bacteriologic response (bacteriological MITT and bacteriological evaluable populations), subjects with missing observations are excluded except for evaluable failures due to the use of concomitant antibiotics. Subjects designated as a failure at a prior visit are not excluded. Additional presentation of the clinical response data with the missing values included and set to failure and set to cure are provided for the clinical MITT population.

- Visit Windows

Day 1 (Baseline) is the first day of treatment. For analysis purposes, the windows for evaluability are defined as follows:

<u>Visit</u>	<u>Day Range</u>
Baseline (Day 1)	N/A
EOT (Visit 3)	6 to 12
EOS (Visit 4)	22 to 36

Prior and Concomitant Medications:

Previous antimicrobial therapy and concomitant medications are listed and summarized for the safety subjects using a modified British National Formulary (BNF) medication dictionary provided by the Applicant. Medications are summarized by the number and percentage of subjects in each treatment group receiving each medication at the therapeutic level (second BNF level) and class level (third BNF level). Percentages are computed for the therapeutic level. Subjects are only counted once at either level if they were taking more than one medication at that level. No inferential statistics are computed.

- Data Sets Analyzed

Two populations are analyzed for efficacy:

- 1) The MITT population which is further defined as the clinical MITT and the bacteriological MITT populations, and
- 2) The efficacy evaluable population which is further defined as the clinical evaluable and bacteriological evaluable populations.

**TABLE 3\*** shows the number of subjects that are included in each efficacy population.

	<u>Data Sets Analyzed</u>	
	<u>Azith 3-Day</u> N (%)	<u>Azith 6-Day</u> N (%)
<b>Total Number of Subjects Treated</b>	281 (100.0)	255 (100.0)
<b>MITT Populations</b>		
Clinical MITT Population	281 (100.0)	254 (99.6)
Bacteriological MITT Population	74 (26.3)	92 (36.1)
<b>Efficacy Evaluable Populations</b>		
<b>Clinical Evaluable Population</b>		
Visit 3 (EOT)	257 (91.5)	233 (91.4)
Visit 4 (EOS)	254 (90.4)	230 (90.2)
<b>Bacteriological Evaluable Population</b>		
Visit 3 (EOT)	71 (25.3)	88 (34.5)
Visit 4 (EOS)	68 (24.2)	84 (32.9)

\* Adopted from EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Table found on Page 48.

The bacteriological populations analyzed for efficacy are higher for the Azith 6-Day regimen compared to the Azith 3-Day regimen.

The clinical response by baseline pathogen for bacteriological MITT subjects is presented in TABLE 4.

**TABLE 4\*** Clinical Response by Baseline Pathogen – Bacteriological MITT Subjects

	Azith 3-Day	Azith 6-Day
EOT; n/N (% Success)		
<i>H. influenzae</i>	28/32 (87.5)	27/28 (96.4)
<i>S. pneumoniae</i>	23/26 (88.5)	39/42 (92.9)
<i>M. catarrhalis</i>	14/15 (93.9)	19/19 (100.0)
<i>S. aureus</i>	2/2 (100.0)	6/6 (100.0)
EOS; n/N (% Cure)		
<i>H. influenzae</i>	24/32 (75.0)	24/28 (85.7)
<i>S. pneumoniae</i>	21/25 (84.0)	34/42 (81.0)
<i>M. catarrhalis</i>	13/15 (92.9)	15/19 (78.9)
<i>S. aureus</i>	2/2 (100.0)	6/6 (100.0)

\* Adopted from EDR NDA 50-784, EDR, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Table 5.2.5.1 found on Page 51.

EOT Success = Cure+ Improvement, EOS Success = Cure.  
 n/ N = number of subjects with clinical success/ number of subjects evaluable at that time point.

The clinical responses (EOS, % Cure) by baseline pathogen for the bacteriological MITT subjects are higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.9%) vs. 15/19 (78.9%). For *Haemophilus influenzae* it was lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low.

One hundred sixty-six subjects (74 azith 3-day; 92 azith 6-day) are included in the bacteriological MITT analyses. The bacteriological success at EOT and EOS are shown in TABLE 5.

**TABLE 5\*** shows the Overall Bacteriological Response – MITT Subjects

	Azith 3-Day	Azith 6-Day
EOT—Visit 3; N (% Success)	66 (89.2%)	88 (95.7%)
EOS—Visit 4; N (% Success)	60 (83.3%)	77 (83.7%)

\* Adopted from EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Bottom Table found, on Page 53.

The overall bacteriological responses (EOS, Visit 4, % Success) for the MITT population are almost identical for the Azith 3-Day and Azith 6-Day regimens.

The bacteriological success rates at EOT and EOS by baseline pathogen for the bacteriological MITT subjects is shown in TABLE 6.

**TABLE 6** Bacteriological Response by Baseline Pathogen – Bacteriological MITT Subjects

	Azith 3-Day	Azith 6-Day
EOT; n/N (% Success)		
<i>H. influenzae</i>	28/32 (87.5)	27/28 (96.4)
<i>S. pneumoniae</i>	23/26 (88.5)	39/42 (92.9)
<i>M. catarrhalis</i>	14/15 (93.3)	19/19 (100.0)
<i>S. aureus</i>	2/2 (100.0)	6/6 (100.0)
EOS; n/N (% Success)		
<i>H. influenzae</i>	25/32 (78.1)	24/28 (85.7)
<i>S. pneumoniae</i>	21/25 (84.0)	34/42 (81.0)
<i>M. catarrhalis</i>	13/15 (92.9)	15/19 (78.9)
<i>S. aureus</i>	2/2 (100.0)	6/6 (100.0)

\* Adopted from EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Bottom Table found, on Page 10.

Success = Documented Eradication + Presumed Eradication  
 n/ N = number of subjects with bacteriological success/ number of subjects evaluable at that time point.

The bacteriological responses (EOS, % Success) by baseline pathogen for the bacteriological MITT population are higher for the following baseline pathogens for the Azith 3-Day regimen : *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.%) vs. 15/19 (78.9%). For *Haemophilus influenzae* it was lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low.

The bacteriological responses by baseline pathogen for the bacteriological evaluable subjects are presented in TABLE 7.

**TABLE 7** shows the success rates at EOT and EOS by baseline pathogen for the bacteriological evaluable subjects

Bacteriological Response by Baseline Pathogen— Bacteriological Evaluable Subjects		
	Azith 3-Day	Azith 6-Day
<b>EOT; n/N (% Success)</b>		
<i>H. influenzae</i>	27/31 (87.1)	25/26 (96.2)
<i>S. pneumoniae</i>	23/26 (88.5)	38/41 (92.7)
<i>M. catarrhalis</i>	13/14 (92.9)	18/18 (100.0)
<i>S. aureus</i>	1/1 (100.0)	6/6 (100.0)
<b>EOS; n/N (% Success)</b>		
<i>H. influenzae</i>	23/30 (76.7)	20/24 (83.3)
<i>S. pneumoniae</i>	21/25 (84.0)	32/40 (80.0)
<i>M. catarrhalis</i>	12/13 (92.3)	13/17 (76.5)
<i>S. aureus</i>	1/1 (100.0)	6/6 (100.0)

Adopted from EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Table found on Page 55.

Success = Documented Eradication + Presumed Eradication.

n/ N = number of subjects with bacteriological success/ number of subjects evaluable at that time point.

The success rates at EOS (EOS, % Success) by baseline pathogen for the bacteriological evaluable population is higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 32/40 (80.0%) and *Moraxella catarrhalis*, 12/13 (92.3%) vs. 13/17 (76.5%). For *Haemophilus influenzae* isolates it is lower: 23/30 (76.7%) vs. 20/24 (83.3%). *Staphylococcus aureus* is the same for both regimens: 1/1 (100%) vs. 6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low.

Baseline Susceptibility to Azithromycin:

Baseline susceptibility of pathogens isolated from the bacteriological MITT subjects are presented, as follows:

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PFIZER INC.

ZITHROMAX® (azithromycin) 500 mg Film-Coated Tablet

**TABLE 8\*** shows AZITHROMYCIN Protocol A0661057, Baseline Susceptibility to Azithromycin - Bacteriological MITT Population

Baseline Pathogens	-----Azithromycin 3-Day-----					-----Azithromycin 6-Day-----				
	Not Tested	Total	S	I	R	Not Tested	Total	S	I	R
H. Influenzae	1	31	31	-	-	2	26	26	-	-
S. Pneumoniae	1	25	22	0	3	1	41	33	0	8
M. Catarrhalis	0	15	15	-	-	0	19	19	-	-
S. Aureus	0	2	2	0	0	0	6	4	0	2

S. Aureus colony count >= 10\*\*4 CFU/ml  
 Azithromycin MIC: Susceptible (S) Intermediate (I) Resistant (R)  
 H. Influenzae <=4  
 S. Pneumoniae <=0.5 1 >=2  
 M. Catarrhalis <=4  
 S. Aureus <=2 4 >=8  
 Source Data: Section 13, Table 2.4 Date of Reporting Dataset Creation: 09OCT2002 Date of Table Generation: 10OCT2002 (11.59)

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Adopted from EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Table found on Page 168.

Overall, 57 isolates of *Haemophilus influenzae*, 66 of *Streptococcus pneumoniae*, 34 of *Moraxella catarrhalis*, and 8 of *Staphylococcus aureus* are evaluated for susceptibility. The majority of isolates are susceptible to azithromycin with the exception of 11/66 (17%) isolates of *Streptococcus pneumoniae* and 2/8 (25%) isolates of *Staphylococcus aureus* that are resistant.

Baseline susceptibility by geographical area is found in EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581\1.0\Approved\27-Jan-2003 16:10, TABLES found on Pages 169 to 172.

In the US, 24 isolates of *Haemophilus influenzae*, 31 of *Streptococcus pneumoniae*, 11 of *Moraxella catarrhalis*, and 6 of *Staphylococcus aureus* are evaluated for susceptibility. With the exception of 4/31 (13%) *Staphylococcus pneumoniae* isolates and 1/6 (17%) *Staphylococcus aureus* isolate, all isolates are susceptible to azithromycin. At non-US sites, 33 isolates of *Haemophilus influenzae*, 35 of *Streptococcus pneumoniae*, 23 of *Moraxella catarrhalis*, and 2 of *Staphylococcus aureus* are evaluated for susceptibility. With the exception of 7/35 (20%) *Streptococcus pneumoniae* isolates and 1/2 (50%) *Staphylococcus aureus* isolate, all isolates are susceptible to azithromycin.

A cross tabulation of MIC and zone susceptibility for MITT bacteriological subjects is presented in TABLE 9. Assessment of susceptibility by MIC size was consistent with assessment by zone size.

**TABLE 9\*** shows a Cross Tabulation of Azithromycin Baseline MIC and Zone Size - Bacteriological MITT Population

Baseline MIC	Baseline Zone Size					Baseline Zone Size				
	Total	S	I	R	Missing	Total	S	I	R	Missing
<i>H. influenzae</i>										
Susceptible	21	21	0	0	0	21	21	0	0	0
Intermediate	0	0	0	0	0	0	0	0	0	0
Resistant	0	0	0	0	0	0	0	0	0	0
Missing	1	0	0	0	1	2	1	0	0	1
<i>S. pneumoniae</i>										
Susceptible	22	22	0	0	0	22	22	0	0	0
Intermediate	0	0	0	0	0	0	0	0	0	0
Resistant	2	0	0	2	0	9	0	0	0	0
Missing	1	0	0	0	1	1	0	0	0	1
<i>M. catarrhalis</i>										
Susceptible	15	15	0	0	0	19	19	0	0	0
Intermediate	0	0	0	0	0	0	0	0	0	0
Resistant	0	0	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0
<i>S. aureus</i>										
Susceptible	3	3	0	0	0	4	4	0	0	0
Intermediate	0	0	0	0	0	0	0	0	0	0
Resistant	0	0	0	0	0	2	0	0	2	0
Missing	0	0	0	0	0	0	0	0	0	0

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*S. aureus* colony count  $\leq 10^8$  CFU/ml  
 Azithromycin MIC, Susceptible Intermediate Resistant Zone, Susceptible Intermediate Resistant  
*H. influenzae*  $\leq 4$  - -  $\leq 12$  - -  
*S. pneumoniae*  $\leq 0.5$  1 -  $\leq 2$   $\leq 12$  - -  
*M. catarrhalis*  $\leq 4$  - -  $\leq 19$  14-17  $\leq 12$   
*S. aureus*  $\leq 2$  4 -  $\leq 8$   $\leq 18$  14-17  $\leq 12$   
 Source Data, Section 13, Table 2.4 Date of Reporting Database Creation: 09OCT2002 Date of Table Generation: 10OCT2003 (13.07)

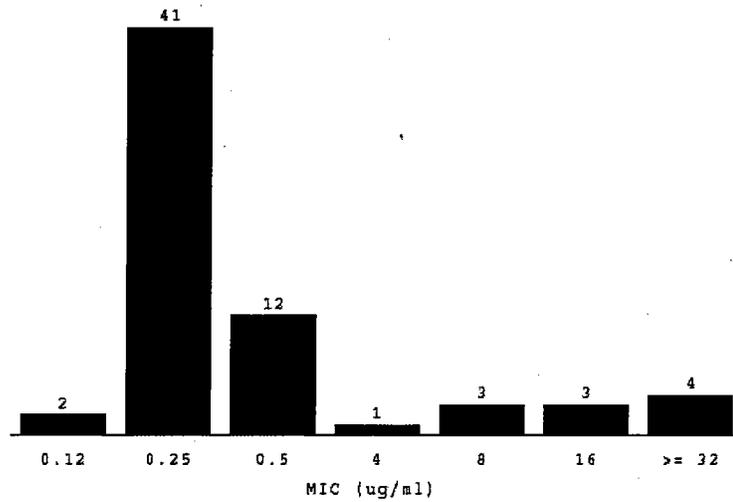
Adopted from EDR NDA 50-784, 03/30/03, Final Study Report: Azithromycin Protocol A0661057, 01000002156581 \ 1.0 \ Approved \ 27-Jan-2003 16:10, Table found on Page 178.

The susceptibility data, results, and conclusions are *acceptable*. In the *Microbiology Summary*, the Applicant indicated a susceptible MIC as  $\leq 2$   $\mu\text{g/mL}$  for *Moraxella catarrhalis*. The Tables on pages 178 and 179 show a susceptible MIC for *Moraxella catarrhalis* is  $\leq 4$   $\mu\text{g/mL}$ . There are no established FDA susceptibility interpretative criteria for *Moraxella catarrhalis*. The raw data actually show *Moraxella catarrhalis* isolates at a susceptibility  $\leq 0.06$   $\mu\text{g/mL}$ . Therefore, the microbiology outcomes and conclusions remain the same.

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***Streptococcus pneumoniae***

**FIGURE 1\*** AZITHROMYCIN Protocol A0661057: Distribution of Number of Baseline Isolates (*Streptococcus pneumoniae*) by Azithromycin MIC value - Safety Population

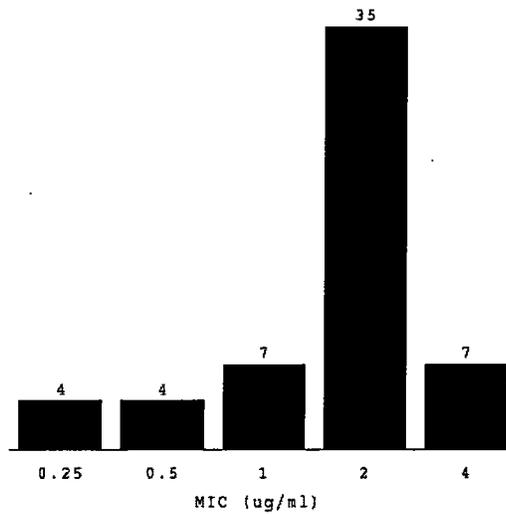


\* Clinical Microbiology, Item 7, Figure 9 (Appendix 2), Source Data: Section 13, Table 2.4 Date of Reporting Dataset Creation: 09OCT2002 Date of Table Generation: 10OCT2002 (12:49)

The aforementioned Figure 1 shows azithromycin MICs for the 66 pneumococcal isolates tested for susceptibility. 83% (55/66) are susceptible to azithromycin with MICs  $\leq 0.5$   $\mu\text{g/mL}$ . Ten isolates (5%) demonstrated high MICs of 8 to  $> 32$   $\mu\text{g/mL}$ .

***Haemophilus influenzae***

**FIGURE 2\*** AZITHROMYCIN Protocol A0661057: Distribution of Number of Baseline Isolates (*Haemophilus Influenzae*) by Azithromycin MIC value - Safety Population

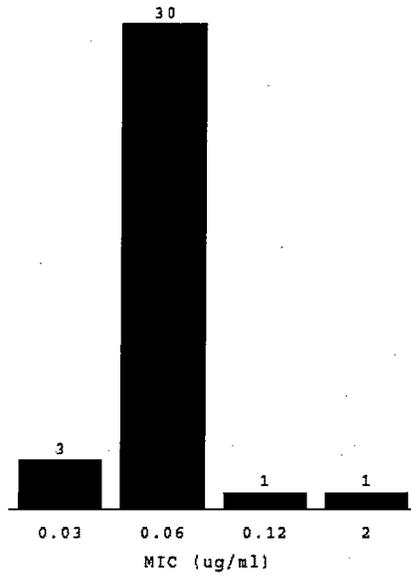


\* Clinical Microbiology, Item 7, Figure 10 (Appendix 2), Source Data: Section 13, Table 2.4 Date of Reporting Dataset Creation: 09OCT2002 Date of Table Generation: 10OCT2002 (12:41)

The aforementioned Figure 2 shows azithromycin MICs for the 57 *Haemophilus influenzae* isolates tested for susceptibility in the study. All 57 have MICs within the susceptible limit for azithromycin ( $\leq 4 \mu\text{g/mL}$ ).

***Moraxella catarrhalis***

**FIGURE 3\*** AZITHROMYCIN Protocol A0661057: Distribution of Number of Baseline Isolates (*Moraxella catarrhalis*) by Azithromycin MIC value - Safety Population

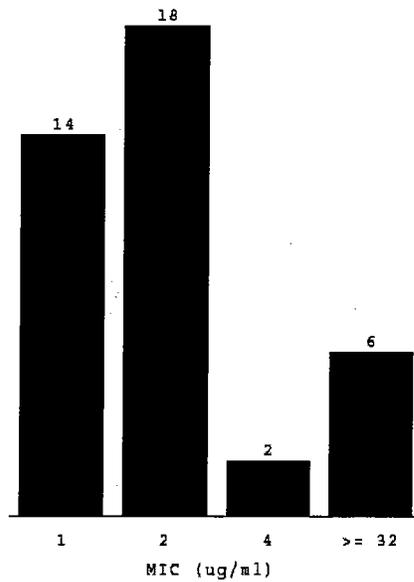


\* Clinical Microbiology, Item 7, Figure 11 (Appendix 2), Source Data: Section 13, Table 2.4 Date of Reporting Dataset Creation: 09OCT2002 Date of Table Generation: 10OCT2002 (12:42)

The aforementioned Figure 3 shows azithromycin MICs for the 35 *Moraxella catarrhalis* isolates tested for susceptibility in the study. MICs ranged from 0.03 to 2 µg/mL, with 86% of the strains having an MIC of 0.06 µg/mL.

***Staphylococcus aureus***

**FIGURE 4\*** AZITHROMYCIN Protocol A0661057: Distribution of Number of Baseline Isolates (*Staphylococcus aureus*) by Azithromycin MIC value - Safety Population



\* Clinical Microbiology, Item 7, Figure 12 (Appendix 2), Source Data: Section 13, Table 2.4 Date of Reporting Dataset Creation: 09OCT2002 Date of Table Generation: 10OCT2002 (12:42)

The aforementioned Figure 4 shows azithromycin MICs for the 40 *Staphylococcus aureus* isolates tested for susceptibility in the study. MICs are 1 (14), 2 (18), 4 (2) or > 32 (6) µg/mL. These 40 *Staphylococcus aureus* isolates represent all baseline isolates, regardless of colony counts, which are tested for susceptibility.

### **Clinical Microbiology Reviewer's Comments on Protocol #A0661057**

The clinical responses (EOS, % Cure) by baseline pathogen for the bacteriological MITT subjects are higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.9%) vs. 15/19 (78.9%). For *Haemophilus influenzae* it was lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low. [See Table 4]

The overall bacteriological responses (EOS, Visit 4, % Success) for the MITT population are almost identical for the Azith 3-Day and Azith 6-Day regimens. [See Table 5]

The bacteriological responses (EOS, % Success) by baseline pathogen for the bacteriological MITT population are higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 34/42 (81.0%) and *Moraxella catarrhalis*, 13/15 (92.9%) vs. 15/19 (78.9%). For *Haemophilus influenzae* it was lower: 24/32 (75.0%) vs. 24/28 (85.7%). *Staphylococcus aureus* is the same for both regimens: 2/2 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low. [See Table 6]

The success rates at EOS (EOS, % Success) by baseline pathogen for the bacteriological evaluable population is higher for the following baseline pathogens for the Azith 3-Day regimen: *Streptococcus pneumoniae*, 21/25 (84.0%) vs. 32/40 (80.0%) and *Moraxella catarrhalis*, 12/13 (92.3%) vs. 13/17 (76.5%). For *Haemophilus influenzae* isolates it is lower: 23/30 (76.7%) vs. 20/24 (83.3%). *Staphylococcus aureus* is the same for both regimens: 1/1 (100%) vs. 6/6 (100%); however, the numbers of *Staphylococcus aureus* isolates are low. [See Table 7]

For subjects with baseline isolates, the bacteriological success rates are high (azith 3-day: 87% to 93% at EOT and 73% to 100% at EOS; azith 6-day: 93% to 100% at EOT and 77% to 100% at EOS) irrespective of the pathogen. The bacteriological success rates in subjects with *Haemophilus influenzae* are slightly higher when azithromycin is administered for 6 days.

One hundred sixty-six subjects (74 azith 3-day; 92 azith 6-day) are included in the bacteriological MITT analyses. For the bacteriological evaluable analysis, 159 subjects (71 azith 3-day; 88 azith 6-day) are included in the EOT analysis and 152 subjects (68 azith 3-day; 84 azith 6-day) are included in the EOS analysis. Similar to the clinical MITT and clinical evaluable analyses, the results from the bacteriological MITT and bacteriological evaluable analyses demonstrated that the overall bacteriological success rates are close whether azithromycin is administered over 3 or 6 days.

### **Clinical Microbiology Reviewer's Conclusions on Protocol #A0661057**

In conclusion, the bacteriological results for *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* isolates are *acceptable* for treatment of acute bacterial sinusitis (ABS) for 3-Days using azithromycin. Overall, the bacteriological results are higher for *Streptococcus pneumoniae* and *Moraxella catarrhalis* using the 3-Day azithromycin regimen. The

6-Day azithromycin regimen gives higher bacteriological results against *Haemophilus influenzae* isolates. However, the bacteriological results using the 3-Day azithromycin regimen are *acceptable*. The numbers of *Staphylococcus aureus* isolates are too few to make any definitive comment.

## V. CONCLUSIONS

The Clinical Microbiology Reviewer concurs with the interpretation and conclusions on the submitted microbiological data for NDA 50-784/SE1-004 on azithromycin treatment for acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

The **DESCRIPTION** section, **MICROBIOLOGY** section and **REFERENCES** section of the Package Labeling for NDA 50-784/SE1-004 all follow the previously approved NDA 50-784 labeling for the 500 mg film-coated tablets, approved May 24, 2002. However, the **REFERENCES** section, is outdated and is made current.

The Applicant submitted the following ZITHROMAX® labeling, 70-5179-00-1.1, Revised January 3003.

## VI. PACKAGE INSERT LABELING

### Clinical Microbiology Reviewer's Comments and Recommendations on the Final Labeling for NDA 50784

#### **DESCRIPTION** section:

ZITHROMAX® (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration.

The aforementioned labeling statement is correct.

#### **MICROBIOLOGY** section:

**Microbiology:** Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

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

#### **Aerobic and facultative gram-positive microorganisms**

*Staphylococcus aureus*  
*Streptococcus agalactiae*  
*Streptococcus pneumoniae*

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*Streptococcus pyogenes*

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

**Aerobic and facultative gram-negative microorganisms**

*Haemophilus ducreyi*

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Neisseria gonorrhoeae*

**“Other” microorganisms**

*Chlamydia pneumoniae*

*Chlamydia trachomatis*

*Mycoplasma pneumoniae*

Beta-lactamase production should have no effect on azithromycin activity.

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

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for azithromycin. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

**Aerobic and facultative gram-positive microorganisms**

Streptococci (Groups C, F, G)

Viridans group streptococci

**Aerobic and facultative gram-negative microorganisms**

*Bordetella pertussis*

*Legionella pneumophila*

**Anaerobic microorganisms**

*Peptostreptococcus* species

*Prevotella bivia*

**“Other” microorganisms**

*Ureaplasma urealyticum*

**Susceptibility Testing Methods section:**

**Susceptibility Testing Methods**

When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could 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 antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1,3</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 1.

**Diffusion techniques:**

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>2,3</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15- $\mu$ g azithromycin to test the susceptibility of microorganisms to azithromycin. The disk diffusion interpretive criteria are provided in Table 1.

**Table 1. Susceptibility Interpretive Criteria for Azithromycin**

<u>Pathogen</u>	<u>Minimum Inhibitory Concentrations (<math>\mu</math>g/mL)</u>			<u>Disk Diffusion (zone diameters in mm)</u>		
	<u>S</u>	<u>I</u>	<u>R<sup>a</sup></u>	<u>S</u>	<u>I</u>	<u>R<sup>a</sup></u>
<i>Haemophilus</i> spp.	$\leq 4$	--	--	$\geq 12$	--	--
<i>Staphylococcus aureus</i>	$\leq 2$	4	$\geq 8$	$\geq 18$	14-17	$\leq 13$
Streptococci including <i>Streptococcus pneumoniae</i> <sup>b</sup>	$\leq 0.5$	1	$\geq 2$	$\geq 18$	14-17	$\leq 13$

<sup>a</sup>. The current absence of data on resistant strains 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.

<sup>b</sup>. Susceptibility of streptococci including *S. pneumoniae* to azithromycin and other macrolides can be predicted by testing erythromycin.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae*. This species is not usually tested.

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound 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 which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of

“resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

**QUALITY CONTROL:**

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard azithromycin powder should provide the following range of values noted in Table 2. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

**Table 2. Acceptable Quality Control Ranges for Azithromycin**

<u>QC Strain</u>	<u>Minimum Inhibitory Concentrations (µg/mL)</u>	<u>Disk Diffusion (zone diameters in mm)</u>
<i>Haemophilus influenzae</i> ATCC 49247	1.0-4.0	13-21
<i>Staphylococcus aureus</i> ATCC 29213	0.5-2.0	
<i>Staphylococcus aureus</i> ATCC 25923		21-26
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06-0.25	19-25

**REFERENCES section:**

The **REFERENCE** section is made current and updated as follows:

Clinical Microbiology Reviewer's Revisions and Changes

- Clinical Microbiology Reviewer's comments (shaded yellow)
- Additions are shown with a single underline (shaded yellow)
- Deletions are shown with a ~~strike through~~ (shaded yellow)

**REFERENCES:**

1. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically* – ~~Fifth~~ Sixth Edition. Approved Standard NCCLS Document M7-A5 6, Vol. 20 23, No. 2 (ISBN 1-56238-394 486-9-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2000 3.

To read as:

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 (ISBN 1-56238-486-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.

1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests – Seventh Edition*. Approved Standard NCCLS Document M2-A7 8, Vol. 20 3, No. 1 (ISBN 1-56238-393 485-0 6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2000 3.

To read as:

2. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests – Eight Edition*. Approved Standard NCCLS Document M2-A8, Vol. 3, No. 1 (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.
3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing – Eleventh Thirteenth Informational Supplement*. NCCLS Document M100-S14 3 [M7-6/M2-A8], Vol. 21, No. 1 (ISBN 1-56238-426-0). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2004 3.

To read as

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

cc: Orig. NDA 50-784/50-710/50-711  
HFD-520/TLMO/J.Alexander  
HFD-520/MO/N.Moledina  
HFD-520/BioPharm/C.Bonapace  
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**RD#1 Initialed 12/16/03 ATS**  
HFD-520/DepDir/L.Gavrilovich

## VII. BIBLIOGRAPHY

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