

**FDA Briefing Package:  
Zithromax<sup>®</sup> (Azithromycin) Oral Suspension  
Single-Dose and Three-Day Treatment of Acute Otitis Media**

Anti-Infective Drugs Advisory Committee  
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## List of Abbreviations

AE – Adverse Event

Amox/Clav – Amoxicillin and Clavulanic Acid

AOM – Acute Otitis Media

AUC<sub>0-∞</sub> – Area under the Serum Concentration-Time Curve

AUC<sub>0-24</sub> – Area under the Serum Concentration-Time Curve for 24 Hours

Azi – Azithromycin

CFTX – Ceftriaxone

EOT – End-of-Therapy Visit

IM – Intramuscular

MIC – Minimum Inhibitory Concentration

MITT – Modified Intent-to-Treat Population

TM – Tympanic Membrane

TOC – Test-of-Cure Visit

## Glossary of Terms

The following definitions are provided as terms that identify consistent features of particular study designs used in AOM trials. These terms will be used in this briefing package and during the advisory committee meeting for consistency and for ease of reference to particular designs.

Clinical-Only Study – A comparative study of antibiotics for the treatment of AOM that does not include the use of tympanocentesis. Subjects are enrolled in the study based on the presence of clinical signs and symptoms of AOM. Outcome is based on resolution or improvement of clinical signs and symptoms at time points following completion of antimicrobial treatment. The objective of this study is to demonstrate similar clinical outcomes for a test drug and comparator at a defined time point.

Microbiologic studies include tympanocentesis for isolation of bacterial pathogens from middle ear fluid. These studies fall into two categories:

Single-Tap Study – A study, often non-comparative, in which tympanocentesis is performed at study entry. Subjects are enrolled based on clinical signs and symptoms, and tympanocentesis is performed to identify patients with bacterial pathogens. Outcome is based on resolution or improvement of clinical signs and symptoms at time points following completion of antibiotic treatment, similar to clinical only studies. The objective of the study is to demonstrate favorable clinical outcomes in subjects with pathogens identified by tympanocentesis at study entry.

Double-Tap Study – A study in which tympanocentesis is performed at study entry and during therapy. Subjects are enrolled based on clinical signs and symptoms, and tympanocentesis is performed to identify patients with bacterial pathogens. Outcome is based on eradication of pathogens from a second tympanocentesis performed within a few days (typically 3-6) after study entry. Clinical outcome at later visits may also be assessed. The objective of the study is to demonstrate favorable rates of bacterial eradication in subjects with pathogens identified by tympanocentesis at study entry.

## Background

Zithromax<sup>®</sup> (azithromycin) has been approved in the United States with a 5-day dosing regimen for the treatment of a number of infectious diseases, including acute exacerbation of chronic bronchitis, pharyngitis/tonsillitis, community-acquired pneumonia, and uncomplicated skin and skin structure infections in adults, as well as acute otitis media and pharyngitis/tonsillitis in children. In adults, the recommended total dose of azithromycin administered over 5 days is 1,500 mg (500 mg on day 1 and 250 mg on days 2-5). In children, the recommended total dose of azithromycin administered over the 5 days is 30 mg/kg (10mg/kg on day 1 and 5 mg/kg on days 2-5) to treat acute otitis media. This will be referred to as the five-day regimen throughout this document. These approvals were based on data demonstrating the safety and effectiveness of azithromycin compared with standard regimens approved for the treatment of these conditions. The studies supporting use of this five-day regimen for treatment of AOM are described in the clinical studies section of the label for Zithromax<sup>®</sup> oral suspension. Excerpted information from the label is provided as Reference 1.

The application under review seeks to shorten the duration of treatment for AOM. The same total dose of azithromycin (30 mg/kg) given in the five-day regimen is proposed to be given in one or three days. In the one-day treatment regimen, a single dose of 30 mg/kg of azithromycin is given. The three-day treatment regimen gives 10 mg/kg of azithromycin once daily for three days. Pfizer, Inc. has submitted the following pivotal studies for approval of the one-day and three-day treatment regimens.

### Pivotal Studies for this Application

Otitis Media Studies	Design	Azi Dose	Azi Duration	Comparators
A0661014	Clinical-Only, Double-Blind	10 mg/kg	3 days	Amox/Clav (Augmentin <sup>®</sup> )
R-0581	Clinical-Only, Double-Blind	30 mg/kg	Single Dose	Amox/clav
A0661015	Single-Tap, Open-label	30 mg/kg	Single Dose	None

Additional supportive evidence from a single-tap study (AZM-NY-95-001) performed at a single center in Costa Rica was submitted. This study compared the one-day and three-day regimens to ceftriaxone for treatment of AOM.

## Microbiology

The class of antimicrobials known as the macrolides includes azithromycin, erythromycin, clarithromycin, and dirithromycin. Azithromycin is a member of the azalide subclass of macrolides and is proposed for treatment of acute otitis media caused by *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. The microbiological information of interest is the spectrum of azithromycin versus these potential pathogens, and the mechanisms of resistance mediated by these pathogens that may affect efficacy.

### **In vitro spectrum of activity**

The table on the following page provides a brief summary representing the in vitro susceptibility of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* to azithromycin. The *S. pneumoniae* susceptibility profile represents isolates from U. S. medical centers from 1996-1997 and 1999-2000. These and other surveillance studies suggest that susceptibility and resistance profiles for these agents of the macrolide class are virtually identical to each other and justify the use of erythromycin susceptibility testing for other members of this class. These surveillance studies, performed at sequential intervals of time, also show that macrolide, and thus azithromycin resistance is increasing, especially in the penicillin intermediate and resistant strains. Surveillance studies also demonstrate that erythromycin resistant rates vary from 6.1% to 53.7% in participating medical centers and that approximately 25% of the *S. pneumoniae* are resistant to macrolides.<sup>1</sup>

At least 8 U. S. surveillance studies for *Haemophilus influenzae* and 4 for *Moraxella catarrhalis* have been performed in the last 15 years. The results of current studies of community acquired respiratory tract isolates<sup>3</sup> and isolates from outpatient clinics<sup>4</sup> are presented in Table 1 and clearly show that greater than 90 percent of the isolates examined remain susceptible to azithromycin at the current breakpoint. Less than 0.3 percent of the *Haemophilus influenzae* isolates have been shown to be resistant to azithromycin.

### **Mechanisms of Action**

Azithromycin acts by binding reversibly to the 23S rRNA component of the 50S ribosomal subunit of susceptible microorganisms, thereby blocking the translocation reaction of polypeptide chain elongation.

### **Mechanisms of Resistance**

Point mutation or modification (methylation) of the target site resulting in reduced affinity of the drug to the target mediates resistance to macrolides in clinical pathogens. Resistance is also mediated by decreased permeability (efflux) resulting in decreased drug concentration. Finally, it may be due to modification of the antimicrobial (esterases, acetyltransferase, and phosphotransferase) resulting in inactivation of the macrolide. Of these resistant mechanisms, modification of the target site, 23S ribosomal RNA, by

methylation (erythromycin resistance methylase, *erm*) and efflux (*mef(A)*) are found in the pathogens of interest.

The two predominant macrolide resistance mechanisms in *S. pneumoniae* are expression of the *mef(A)* and *erm(B)* genes. In the U.S. the predominant resistant determinant appears to be *mef(A)*, accounting for ~66.5% macrolide resistance. Generally, strains with *mef(A)* have erythromycin (EM) MICs of 1-32 Fg/mL and clindamycin (CM) MICs #0.125 Fg/mL. Strains with *erm(B)* determinants usually have EM MICs \$64 Fg/mL and CM MICs \$8.0 Fg/mL.

Some *Haemophilus influenzae* and other gram-negative species have innate resistance to macrolides, thought to be mediated by the broad specificity efflux pump AcrAB-TolC. As seen from Table 1, the *Haemophilus influenzae* MIC<sub>90</sub> is 2.0 Fg/mL and shows that a majority of the strains are below the susceptible breakpoint of 4 Fg/mL.

Azithromycin in vitro spectrum of activity for select pathogens

Pathogen	# strains	MIC range	MIC <sub>50</sub>	MIC <sub>90</sub>	Ref
<i>S. pneumoniae</i>	1531	#0.03 - >64	0.12	16.0	1
PEN <sup>S</sup>	1008	#0.03 - >64	0.12	0.25	
PEN <sup>I</sup>	194	#0.03 - >64	0.25	>64	
PEN <sup>R</sup>	329	#0.06 - >64	8.0	>64	
EM	1531	#0.06 - >64	0.06	8.0	
<i>S. pneumoniae</i>	----	----	----	----	2
PEN <sup>S</sup>	2849	#0.125 - \$64	#0.125	#0.125	
PEN <sup>I</sup>	1059	#0.125 - \$64	#0.125	4.0	
PEN <sup>R</sup>	581	#0.125 - \$64	1.0	\$64	
<i>H. influenzae</i>	1077	#0.125 - >16	2.0	2.0	3
	1032	0.03 - 16	1.0	2.0	4
<i>M. catarrhalis</i>	503	#0.125 - 0.25	#0.125	#0.125	3
	444	#0.03 - >64	0.06	0.12	4

<sup>1</sup> Doren, G. V., K.P. Heilmann, H.K. Huynh, et.al. 2001. Antimicrobial Resistance among Clinical Isolates of *Streptococcus pneumoniae* in the United States during 1999-2000, Including a Comparison of Resistant Rates since 1994-1995. Antimicrob. Agents Chemother. 45:1721-1729.

<sup>2</sup> Mason, E.O. Jr., L.B. Lamberth, N.L. Kershaw, et.al. 2000. *Streptococcus pneumoniae* in the USA: In vitro susceptibility and pharmacodynamic analysis. J. Antimicrob. Chemother. 45:623-631.

<sup>3</sup> Doren, G.V., R.N. Jones, M. A. Pfaller, et.al. 1999. *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with Community-Acquired Respiratory Tract Infections: Antimicrobial Susceptibility Patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada 1997). Antimicrob. Agents Chemother. 43:385-389.

<sup>4</sup> Thornsberry, C., P.T. Ogilvie, H. P. Holley, et. al. 1999. Survey of Susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* Isolates to 26 Antimicrobial Agents: A Prospective U.S. Study. Antimicrob. Agents Chemother. 43:2612-2623.

## Clinical Pharmacology and Biopharmaceutics

The pharmacokinetic parameter that appears to be most predictive of azithromycin efficacy is the ratio of the area under the serum concentration-time curve ( $AUC_{0-\infty}$ ) to the organism's minimal inhibitory concentration (MIC), the  $AUC_{0-\infty}/MIC$  ratio. The concept of accelerated dosing assumes that the pharmacokinetics of azithromycin are linear across the proposed dosing range, resulting in a similar exposure ( $AUC_{0-\infty}$ ) and  $AUC_{0-\infty}/MIC$  by administering the same total dose.

### **Pharmacokinetics in pediatric subjects:**

The pharmacokinetics of azithromycin following the administration of 20 mg/kg/day  $\times$  3 days, 12 mg/kg/day  $\times$  5 days, and 10 mg/kg/day  $\times$  3 days were evaluated in pediatric subjects with pharyngitis/tonsillitis or other bacterial infections. The studies were non-comparative and the 1-day regimen (30 mg/kg) was not evaluated. Blood samples were collected for only 24 hours following the last dose. Thus, the area under the serum concentration-time curve for 24 hrs ( $AUC_{0-24}$ ) following the last dose is the only measure of exposure that can be assessed. The  $AUC_{0-24}$  following the last dose were 3.93, 7.92, and 2.35  $\mu\text{g}\cdot\text{hr}/\text{mL}$  for 20 mg/kg/day, 12 mg/kg/day, and 10 mg/kg/day, respectively. Since the half-life of azithromycin is approximately 68 hours, accumulation is still occurring at day 3 and day 5. After correction for the administered dose, the results demonstrate that the exposure from the 3-day regimen ranged from 28% less to 21% greater than the 5-day regimen. Although the  $AUC_{0-24}$  is similar among the regimens, the reviewer is unable to conclude that the overall exposure ( $AUC_{0-\infty}$ ) from 3-day and 5-day regimens is similar since the studies were not designed to provide this information.

### **Pharmacokinetics in adult subjects (3-day vs. 5-day):**

The pharmacokinetics of azithromycin following the administration of 500 mg/day  $\times$  3 days vs. 500 mg on day 1 followed by 250 mg  $\times$  4 days were evaluated in three comparative studies with healthy adult subjects (066-087, AZM-NY-90-011, and AZM-F-93-004). The data from AZM-NY-90-011 were excluded from the analysis since the accuracy of the analytical methods was outside of the  $\pm 15\%$  acceptable range. Limited blood samples were obtained from study 066-087, excluding the first and last dosing interval, and introduced uncertainty in the results from the non-parametric analysis. Thus, the raw data from study 066-087 were fit to a 3-compartment, oral absorption model using Win Nonlin (version 3.1). The  $AUC_{0-\infty}$  from the 3-day regimen was compared to the 5-day regimen of each study using a geometric mean ratio (GMR, 3-day/5-day) and 90% confidence interval. The GMR (90% confidence interval) for study AZM-F-93-004 was 0.933 (0.798 to 1.092). Thus, the  $AUC_{0-\infty}$  from the 3-day and 5-day regimens was similar. The GMR for study 066-087 using observed and simulated concentrations was 1.185 and 1.118, respectively. The 90% confidence interval exceeded 1.25 in both instances. The two studies support that the  $AUC_{0-\infty}$  associated with a 3-day regimen is similar to a 5-day regimen.

**Pharmacokinetics in adult subjects (1-day vs. 3-day):**

The pharmacokinetics of azithromycin following the administration of 1,500 mg as a single dose vs. 500 mg/day  $\times$  3 days were evaluated in a comparative study with healthy adult subjects (GA2000). The analytical methods in this study had a lower limit of quantitation (LLOQ) approximately 5-fold greater than previous studies, resulting in azithromycin concentrations below the LLOQ within 48 hours in the majority of subjects following a single dose and by the end of each dosing interval in most subjects for the 3-day regimen. Using the data provided, the  $AUC_{0-\infty}$  GMR (90% confidence interval) was 1.235 (0.935 to 1.632) and the sponsor concluded that the exposure from the two regimens was similar. However, the sponsor used azithromycin concentrations below the LLOQ to estimate the terminal elimination rate constant and  $AUC_{0-\infty}$  in both regimens. The reviewer estimated the  $AUC_{0-t}$  using concentrations above the LLOQ. The  $AUC_{0-t}$  GMR was 0.829 but included data from only five subjects. Since the exposure from the 1-day regimen may be less than the 3-day regimen, the reviewer is unable to state that the overall exposure is similar between the two regimens.

**Pharmacokinetics in adult subjects (1-day vs. 5-day):**

The sponsor did not conduct a study comparing the  $AUC_{0-\infty}$  resulting from 1,500 mg as a single dose vs. 500 mg on day 1 followed by 250 mg/day  $\times$  4 days.

## Study A0661014: Clinical-Only Study of Azi Three-Day Treatment vs. Amox/Clav for AOM

Study A0661014 was a double-blind, multicenter, randomized trial comparing 10 mg/kg daily dose of azithromycin for 3 days with a ten-day course of amox/clav (45 mg/kg/day given BID) in the treatment of AOM in children ages 6 months to 12 years. This was a clinical-only study with enrollment of 373 patients from 28 U. S. study sites.

The following table shows the clinical outcomes for the MITT and per protocol populations as reported by the applicant. Outcomes are reported for end of therapy (Study day 8 to 12) and test of cure (Study day 20 to 32) visits.

Study A0661014: Clinical Outcomes

	Azithromycin		Amox/Clav		95% Confidence Interval of Difference
	N	(%)	N	(%)	
<b>MITT Population</b>					
Patients evaluable at EOT	185	(100)	181	(100)	
Success (Cured or Improved)	153	(83)	159	(88)	-12.9, 2.7
Failure	32	(17)	22	(12)	
Patients evaluable at TOC	182	(100)	180	(100)	
Cure	134	(74)	124	(69)	- 5.2, 14.6
Failure	48	(26)	56	(31)	
<b>Per Protocol Population</b>					
Patients evaluable at EOT	166	(100)	151	(100)	
Success (Cured or Improved)	134	(81)	129	(85)	-13.6, 4.2
Failure	32	(19)	22	(15)	
Patients evaluable at TOC	179	(100)	175	(100)	
Cure	131	(73)	120	(69)	- 5.4, 14.7
Failure	48	(27)	55	(31)	
EOT = Day 8 – 12; TOC = Day 20 – 32					

The results of this clinical study support the conclusion that 10 mg/kg/day for 3 days of azithromycin has similar effectiveness to a ten-day course of amoxicillin/clavulanate in the treatment of AOM. The end of therapy and test of cure analyses of the per protocol population support those of the MITT population.

In this study, 114 (31%) of the treated patients were 1 month to 2 years of age, and 259 (69%) were >2 years of age. The following table shows the clinical outcomes by age for the MITT population.

Study A0661014: Clinical Outcomes by Age (MITT Population)

	<b>Azithromycin</b>		<b>Amox/Clav</b>		<b>95% Confidence Interval of Difference</b>
	<b>N</b>	<b>(%)</b>	<b>N</b>	<b>(%)</b>	
<b>Age ≤2 years</b>					
Patients evaluable at EOT	60	(100)	52	(100)	-26.2, 7.0
Success (Cured or Improved)	45	(75)	44	(85)	
Failure	15	(25)	8	(15)	
Patients evaluable at TOC	58	(100)	52	(100)	-17.7, 23.1
Cure	35	(60)	30	(58)	
Failure	23	(40)	22	(42)	
<b>Age &gt;2 years</b>					
Patients evaluable at EOT	127	(100)	129	(100)	-13.1, 4.9
Success (Cured or Improved)	108	(85)	115	(89)	
Failure	19	(15)	14	(11)	
Patients evaluable at TOC	124	(100)	128	(100)	-4.8, 17.6
Cure	99	(80)	94	(73)	
Failure	25	(20)	34	(27)	
EOT = Day 8 – 12; TOC = Day 20 –32					

When outcomes were evaluated by patient age  $\leq 2$  years or  $> 2$  years, response rates between the treatment groups were similar. For both drugs, children  $> 2$  years were more likely to have a successful clinical response than were children  $\leq 2$  years.

This clinical-only study of AOM includes an unknown proportion of patients with sterile middle ear fluid. The results reported here must be correlated with those from microbiologic studies using diagnostic tympanocenteses.

AOM has a high spontaneous resolution rate, and the effect of antimicrobial treatment is limited. Because there was no placebo group in this study, the true effect of the study drugs is unknown.

## Study R-0581: Clinical-Only Study of Azi One-Day Treatment vs. Amox/Clav for AOM

Study R-0581 was a double-blind, double-dummy, multicenter, randomized trial comparing a single 30 mg/kg dose of azithromycin with a ten day course of amoxicillin/clavulanate (45 mg/kg/day given BID) in the treatment of acute otitis media (AOM) in children 6 months to 12 years of age. This was a clinical-only study with enrollment of 350 patients (175 azithromycin, 175 amoxicillin/clavulanate) from nine U.S. study sites.

The following table shows the clinical outcomes for the modified intent-to-treat (MITT) and per protocol populations as reported by the applicant. Outcomes are reported for end of therapy (Study day 12 to 16) and test of cure (Study day 28 to 32) visits.

Study R-0581: Clinical Outcomes

	<b>Azithromycin</b>		<b>Amox/Clav</b>		<b>95% Confidence Interval of Difference</b>
	<b>N</b>	<b>(%)</b>	<b>N</b>	<b>(%)</b>	
<b>MITT Population</b>					
Patients evaluable at EOT	160	(100)	161	(100)	-9.2, 6.5
Success (Cured or Improved)	139	(87)	142	(88)	
Failure	21	(13)	19	(12)	
Patients evaluable at TOC	151	(100)	154	(100)	-10.2, 10.5
Cure	114	(75)	116	(75)	
Failure	37	(25)	38	(25)	
<b>Per Protocol Population</b>					
Patients evaluable at EOT	147	(100)	148	(100)	-9.2, 7.7
Success (Cured or Improved)	127	(86)	129	(87)	
Failure	20	(14)	19	(13)	
Patients evaluable at TOC	144	(100)	142	(100)	-11.8, 9.7
Cure	107	(74)	107	(75)	
Failure	37	(26)	35	(25)	

EOT = End of Therapy (Day 12 to 16); TOC = Test of Cure (Day 28 to 32)

The results of this clinical study support the conclusion that a single 30 mg/kg dose of azithromycin has similar effectiveness to a ten day course of amoxicillin/clavulanate in the treatment of AOM. The end of therapy and test of cure analyses of the per protocol population support those of the MITT population.

In this study, 138 (40%) of the treated patients were  $\leq 2$  years of age, and 208 (60%) were  $> 2$  years of age. The following table shows the clinical outcomes by age for the MITT population.

Study R-0581: Clinical Outcomes by Age (MITT Population)

	<b>Azithromycin</b>		<b>Amox/Clav</b>		<b>95% Confidence Interval of Difference</b>
	<b>N</b>	<b>(%)</b>	<b>N</b>	<b>(%)</b>	
<b>Age <math>\leq 2</math> Years</b>					
Patients evaluable at EOT	68	(100)	56	(100)	-18, 13.7
Success (Cured or Improved)	53	(78)	45	(80)	
Failure	15	(22)	11	(20)	
Patients evaluable at TOC	64	(100)	53	(100)	-12.2, 27.1
Cure	41	(64)	30	(57)	
Failure	23	(36)	23	(43)	
<b>Age <math>&gt; 2</math> Years</b>					
Patients evaluable at EOT	92	(100)	105	(100)	-7.1, 9.3
Success (Cured or Improved)	86	(93)	97	(92)	
Failure	6	(7)	8	(8)	
Patients evaluable at TOC	87	(100)	101	(100)	-12.7, 10.3
Cure	73	(84)	86	(85)	
Failure	14	(16)	15	(15)	
EOT=End of Therapy (Day 12 to 16); TOC=Test of Cure (Day 28 to 32)					

When outcomes were evaluated by patient age  $\leq 2$  years or  $> 2$  years, response rates between the treatment groups were similar. For both drugs, children  $> 2$  years were more likely to have a successful clinical response than were children  $\leq 2$  years.

The same caveats noted with study A0661014 apply to this study. These include the enrollment of patients with sterile middle ear fluid, the need for correlation with microbiologic studies, the high spontaneous resolution rate, and inability to compare outcomes directly to placebo treatment.

## Study A0661015: Single-Tap Study of Azi One-Day Treatment for AOM

Study A0661015 was an open-label, non-comparative, multi-center trial of AOM using a single 30 mg/kg dose of azithromycin in children 6 months to 12 years of age. The study design included tympanocentesis performed at baseline to identify patients with bacterial AOM. Outcomes are based on clinical assessments at specified time points. This study enrolled 248 patients from 22 U. S. and Latin American study sites.

The following table shows the clinical outcomes for the MITT and per protocol populations as reported by the applicant. Outcomes are reported for EOT (Study day 8 to 12) and TOC (Study day 20 to 32) visits.

Study A0661015: Clinical Outcomes

	Azithromycin N (%)	95% Confidence Interval of Point Estimate
<b>MITT Population</b>		
Patients evaluable at EOT	240 (100)	
Success (Cured or Improved)	213 (89)	84.5, 93.0
Failure	27 (11)	
Patients evaluable at TOC	242 (100)	
Cure	206 (85)	80.4, 89.8
Failure	39 (15)	
<b>Per Protocol Population</b>		
Patients evaluable at EOT	215 (100)	
Success (Cured or Improved)	190 (88)	83.9, 92.9
Failure	25 (12)	
Patients evaluable at TOC	229 (100)	
Cure	195 (85)	80.3, 90.0
Failure	34 (15)	
EOT = Day 8 to 12; TOC = Day 20 to 32		

Clinical outcomes in MITT patients with a pathogen identified at the baseline visit are shown in the following table.

Study A0661015: Clinical Outcome by Baseline Pathogen (MITT Population)

<b>EOT Assessment:</b>	<b><i>H. influenzae</i> (N=42)</b>		<b><i>M. catarrhalis</i> (N=10)</b>		<b><i>S. pneumoniae</i> (N=76)</b>	
Outcome	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Success	30 ( 71%)	56.6, 86.3	10 (100%)	95.0, 100	70 (92%)	85.4, 98.8
Cure	18 (43%)		5 (50%)		49 (64%)	
Improvement	12 (29%)		5 (50%)		21 (28%)	
Failure	12 (29%)		0 ( 0%)		6 ( 8%)	
<b>TOC Assessment:</b>	<b><i>H. influenzae</i> (N=44)</b>		<b><i>M. catarrhalis</i> (N=10)</b>		<b><i>S. pneumoniae</i> (N=76)</b>	
Outcome	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Cure	28 (64%)	48.3, 79.0	10 (100%)	95.0, 100	67 (88%)	80.2, 96.1
Failure	16 (36%)		0 ( 0%)		9 (12%)	

Of particular note, 12 of 76 (16%) *S. pneumoniae* isolates were resistant to azithromycin. The clinical success rates at EOT and TOC were 10/12 and 8/12, respectively.

This Single-Tap study demonstrates clinical cure rates at EOT roughly similar to those for azithromycin-treated patients in the “Clinical Only” studies. However, the success rates for patients with *H. influenzae* identified by baseline tympanocentesis are lower than for the overall population. These lower cure rates for patients with *H. influenzae* at baseline are similar to cure rates for patients treated with the approved regimen of azithromycin.

In this study, 86 (35%) of the treated patients were  $\leq 2$  years of age, and 162 (65%) were  $> 2$  years of age. The following table shows clinical outcomes by age for the MITT population.

Study A0661015: Clinical Outcomes by Age (MITT Population)

	Azithromycin		95% Confidence Interval of Point Estimate
	N	(%)	
<b>Age <math>\leq 2</math> years</b>			
Patients evaluable at EOT	82	(100)	
Success (Cured or Improved)	69	(84)	75.6, 92.7
Failure	13	(16)	
Patients evaluable at TOC	83	(100)	
Cure	64	(77)	67.5, 86.7
Failure	19	(23)	
<b>Age <math>&gt; 2</math> years</b>			
Patients evaluable at EOT	158	(100)	
Success (Cured or Improved)	144	(91)	86.4, 95.9
Failure	14	(9)	
Patients evaluable at TOC	159	(100)	
Cure	142	(89)	84.2, 94.4
Failure	17	(11)	
EOT = End of Therapy (Day 8 to 12); TOC = Test of Cure (Day 20 to 32)			

Children  $> 2$  years of age were more likely to have a successful clinical response than were children  $\leq 2$  years. Similar results are seen when patients with a baseline pathogen are grouped by age, as shown in the following table.

Study A0661015: Clinical Outcome by Baseline Pathogen and Age (MITT Population)

EOT Assessment:	<i>H. influenzae</i>		<i>S. pneumoniae</i>	
	$\leq 2$ years	$> 2$ years	$\leq 2$ years	$> 2$ years
Outcome	N (%)	N (%)	N (%)	N (%)
Success	11 (61%)	19 (79%)	23 (92%)	47 (92%)
Failure	7 (39%)	5 (21%)	2 (8%)	4 (8%)
<b>TOC Assessment:</b>				
Outcome	N (%)	N (%)	N (%)	N (%)
Cure	10 (53%)	18 (72%)	20 (80%)	47 (92%)
Failure	9 (47%)	7 (28%)	5 (20%)	4 (8%)

## Study AZM-NY-95-001: Supportive Single-Tap Study of One-Day Azi vs. Three-Day Azi vs. IM Ceftriaxone

Study AZM-NY-95-001 was a single center (Costa Rica) trial of AOM comparing a single 30 mg/kg dose of azithromycin, 10 mg/kg daily of azithromycin for 3 days, and 50 mg/kg of IM CFTX. Initially, the study used a double-dummy, double-blind design, but due to the color of reconstituted CFTX the injection was unblinded. The investigator remained blinded to the dose regimen of azithromycin. This was a single-tap study with outcome assessments at EOT (days 9 to 19) and follow-up (days 26 to 44). One hundred ninety-eight subjects (66 azi single dose; 66 azi 3-day; 66 CFTX) were randomized to treatment. Ninety-eight subjects (30 azi single dose; 35 azi 3-day; and 33 CFTX) had an appropriate pathogen isolated at baseline, and were included in the evaluation of clinical response by baseline pathogen.

Clinical success (cure or improvement) was reported for 93.8% of azi single dose, 92.4% of azi 3-day, and 96.9% of CFTX patients at the follow-up visit.

Clinical outcomes in MITT patients with *H. influenzae* or *S. pneumoniae* at the baseline visit are shown in the following table. There were only two patients with *M. catarrhalis* enrolled in the study. Both patients were treated with the 3-day regimen of azithromycin and both were clinical cures.

Study AZM-NY-95-001: Clinical Outcome by Baseline Pathogen (MITT Population)

<b>EOT Assessment:</b>	<i>H. influenzae</i>			<i>S. pneumoniae</i>		
Outcome	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)
Total Patients	9 (100%)	15 (100%)	10 (100%)	21 (100%)	18 (100%)	23 (100%)
Success	8 (89%)	14 (93%)	10 (100%)	20 (95%)	15 (83%)	23 (100%)
Failure	1 (11%)	1 (7%)	0	0	0	0
Missing	0	0	0	1 (5%)	3 (17%)	0
<b>TOC Assessment:</b>	<i>H. influenzae</i>			<i>S. pneumoniae</i>		
Outcome	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)
Total	9 (100%)	15 (100%)	10 (100%)	21 (100%)	18 (100%)	23 (100%)
Cure	7 (78%)	11 (74%)	9 (90%)	20 (95%)	17 (94%)	23 (100%)
Failure	1 (11%)	2 (13%)	0	0	0	0
Missing	1 (11%)	2 (13%)	1 (10%)	1 (5%)	1 (6%)	0

## Efficacy

The descriptions of the individual clinical studies summarize the outcome information supplied by the applicant in support of the one-day and three-day dosage regimens for treatment of acute otitis media. The clinical studies section of the label for the Zithromax<sup>®</sup> oral suspension (Ref. #1) summarizes the information provided in support of the five-day regimen.

The clinical-only study of the five-day treatment regimen showed clinical outcomes at EOT of 88% for azi and the control agent. Clinical outcomes at TOC were 73% for azi and 71% for the comparator. The clinical-only study for the three-day regimen (study A0661014) showed MITT cure rates of 83% for azi and 88% for amox/clav at EOT. At TOC, the cure rates were 74% for azi and 69% for amox/clav. The clinical-only study for the one-day regimen (study R-0581) showed MITT cure rates of 87% for azi and 88% for amox/clav at EOT. At TOC, the cure rates were 75% in both treatment arms.

The clinical outcomes for patients with *S. pneumoniae* and *H. influenzae* at EOT and TOC for the different treatment regimens are summarized in the following table.

Dose Groups	30 mg/kg – SD (One-Day)	10 mg/kg x 3 (Three-Day)	10 mg/kg – Day 1 5 mg/kg – Days 2-5 (Five-Day)	Comparator
<b>EOT Assessment</b>				
<i>H. influenzae</i>	38/51 (74%)	14/15 (93%)	52/65 (80%)	19/19 (100%)
<i>S. pneumoniae</i>	90/97 (92%)	15/18 (83%)	86/103 (84%)	39/39 (100%)
<b>TOC Assessment</b>				
<i>H. influenzae</i>	35/53 (66%)	11/15 (74%)	38/57 (67%)	15/18 (83%)
<i>S. pneumoniae</i>	87/97 (90%)	17/18 (94%)	62/84 (74%)	41/45 (91%)

In a review of the published literature, there was additional information regarding clinical and microbiologic efficacy from two comparative double-blind studies conducted by Dagan et al. Of particular note are the relatively low bacterial eradication rates for patients with *H. influenzae* treated with azithromycin in both of these studies. The articles, References 2 and 3, are provided in this package for your review.

## Safety

### Number of Subjects Treated Phase 2-4 Studies

As of the June 30, 2000 cutoff date, 2590 subjects received azithromycin in the Phase 2-4 pooled studies. A total of 1897 subjects received other antibiotics in the comparative trials. The number of subjects receiving azithromycin and the individual comparative agents in the U. S./Canada and outside North America in the pooled Phase 2-4 studies is provided below.

Treatment	Number of Subjects Treated		
	U.S./Canadian	Non-North American	Total
Azithromycin	518	2072	2590
Amox/Clav	358	423	781
Penicillin V	0	394	394
Cefaclor	0	315	315
Clarithromycin	0	307	307
Erythromycin	0	19	19
CFTX	0	66	66
Cefixime	0	15	15
TOTAL	876	3611	4487

### Adverse Events

A summary of the most common treatment-related adverse events is presented below for subjects who received azithromycin or a comparator in Phase 2-4 studies. Information on the five-day dose regimen is from the original NDA application. Caution should be taken in making comparisons between the five-day regimen and the shorter duration regimens. Caution should also be taken in making comparisons with all comparator patients, since patients who participated in studies of pharyngitis are included in this group. For instance, part of the reason for a higher frequency of headache in the comparator is likely related to the expected occurrence of that AE in pharyngitis patients.

#### Commonly Reported Treatment-Related Adverse Events (≥5 Subjects in Either Azithromycin or Comparator Group)

Dose Groups	30 mg/kg – SD (One-Day)	10 mg/kg x 3 (Three-Day)	10 mg/kg – Day 1 5 mg/kg – Days 2-5 (Five-Day)	Comparator
Subjects with AE	13.6 (66/487)	8.6 (148/1729)	5.9 (112/1888)	12.1 (230/1897)
<i>Adverse Events</i>				
Vomiting	4.9 (24/487)	2.3 (39/1729)	1.1 (21/1888)	2.4 (92/1897)
Diarrhea	4.3 (21/487)	2.6 (45/1729)	1.8 (33/1888)	8.9 (169/1897)
Abdominal pain	1.4 (7/487)	1.7 (30/1729)	1.2 (22/1888)	2.0 (37/1897)
Nausea	1.0 (5/487)	0.4 (7/1729)	0.5 (9/1888)	1.2 (22/1897)
Rash	1.0 (5/487)	0.6 (10/1729)	0.4 (7/1888)	3.0 (57/1897)
Headache	0.0 (0/487)	0.1 (2/1729)	0.3 (5/1888)	1.1 (21/1897)

Of note in this table, vomiting was reported at a higher frequency in subjects who received the one-day azithromycin regimen. Diarrhea and nausea were also more frequent in this group, though even higher rates were seen in the comparator group. Higher rates of rash and diarrhea among patients in the comparator group are not surprising, since the comparator agents include beta-lactams and Augmentin in particular.

The following table notes the incidence of vomiting and diarrhea by day of onset and azi treatment group. Most of the vomiting noted with the one-day regimen occurs during the first day of treatment.

Percent (n/N) of Subjects Reporting Treatment-Related Vomiting and Diarrhea by Day and Treatment Group

<b>Total Dose</b>	<b>30 mg/kg</b>		
<b>Dose Group</b>	<b>30 mg/kg – SD (One-Day)</b>	<b>10 mg/kg x 3 (Three-Day)</b>	<b>10 mg/kg – Day 1 5 mg/kg – Days 2-5 (Five-Day)</b>
<i>Vomiting</i>			
Overall	4.9 (24/487)	2.3 (39/1729)	1.1 (21/1888)
Day 1	4.7 (23/487)	1.2 (21/1729)	0.5 (9/1888)
Day 2	0.2 (1/487)	0.6 (10/1729)	0.4 (7/1888)
Day 3	0.0 (0/487)	0.1 (2/1729)	0.2 (3/1863)
Day 4	0.0 (0/487)	0.0 (0/1729)	0.0 (0/1857)
Day 5	0.0 (0/487)	0.0 (0/1729)	0.0 (0/1851)
<i>Diarrhea</i>			
Overall	4.3 (21/487)	2.6 (45/1729)	1.8 (33/1888)
Day 1	1.6 (8/487)	0.5 (9/1729)	0.6 (11/1888)
Day 2	1.6 (8/487)	1.0 (17/1729)	0.4 (8/1888)
Day 3	0.4 (2/487)	0.5 (8/1729)	0.4 (7/1863)
Day 4	0.0 (0/487)	0.1 (1/1729)	0.2 (3/1857)
Day 5	0.0 (0/487)	0.1 (2/1729)	0.1 (2/1851)

SD = Single Dose; x3 = 3 days, x5 = 5 days

**Serious Adverse Events:**

Of the 2152 subjects in the studies relevant to the claims, 8 reported serious adverse events. Five of the eight subjects received azithromycin and 3 received a comparator. The events reported by the azithromycin-treated subjects consisted of convulsions, diarrhea, enterocolitis, gastroenteritis, vomiting, dehydration, abscess, pleural effusion and pneumonia. Comparator-treated subjects reported fever, febrile convulsions, abdominal pain, gastroenteritis, vomiting, dehydration, otitis media, and upper respiratory tract infection. All serious adverse events reported by subjects in the studies relevant to the claims were considered unrelated to treatment by the investigator.

## Current AOM Guidance

The following outlines the studies described in the current draft Guidance for Industry on AOM trials. This information is provided to outline the general recommendations made by the FDA to pharmaceutical firms performing AOM studies, and also to generate some discussion about these recommendations during the advisory committee meeting.

The draft Guidance recommends two trials, a clinical only study and a microbiologic study.

### **Clinical only study:**

- Multicenter trial with rigid case definition
- Typically in children  $\geq 6$  months of age
- Baseline tympanocentesis not necessary; however, tympanocentesis of failures strongly encouraged

### **Microbiologic study:**

- At least 2 investigators in geographically diverse areas
- Baseline tympanocentesis necessary for microbiologic etiology
- Repeat tympanocentesis strongly encouraged in therapeutic failures
- $\geq 25$  *S. pneumoniae* (for PRSP, discuss with Division),  $\geq 25$  *H. influenzae*,  $\geq 15$  *M. catarrhalis* from the microbiologic study
- if clinical and microbiologic efficacy against three pathogens not adequate, restricted product to second line therapy

### **Case Definition**

Clinical diagnosis of AOM at entry based on:

1. history and physical examination
2. pneumatic otoscopy findings:  
swollen bulging tympanic membrane (TM) which may be erythematous  
loss of light reflex and TM landmarks, abnormal TM mobility
3. tympanometry or acoustic reflectometry

Exclude patients with tympanostomy tubes, otitis externa but not those with perforated TMs

### **Primary efficacy endpoints**

- Clinical and Microbiologic outcomes at test of cure visit (TOC) 2-4 weeks after study entry
- Microbiologic eradication presumed from the clinical response at TOC visit, for the majority of patients
- Negative culture at the on therapy visit not evidence of documented eradication

A complete copy of the draft guidance on AOM is provided as Reference 4.

## References

1. Excerpted Information from Zithromax<sup>®</sup> Oral Suspension Label
2. Dagan R et al., “Bacteriologic and Clinical Efficacy of Amoxicillin/Clavulanate vs. Azithromycin in Acute Otitis Media” *Pediatric Infectious Diseases Journal* 19(2):95-104, February 2000.
3. Dagan R et al., “Bacteriologic Efficacies of Oral Azithromycin and Oral Cefaclor in Treatment of Acute Otitis Media in Infants and Young Children” *Antimicrobial Agents and Chemotherapy* 44(1):43-50, January 2000.
4. FDA, Center for Drug Evaluation and Research, DRAFT Guidance for Industry “Acute Otitis Media – Developing Antimicrobial Drugs for Treatment” July 1998.
5. Marchant CD et al., “Measuring the Comparative Efficacy of Antibacterial Agents for Acute Otitis Media: The Pollyanna Phenomenon” *The Journal of Pediatrics* 120(1):72-77, January 1992.
6. Klein JO et al., “Microbiologic Efficacy of Antibacterial Drugs for Acute Otitis Media” *Pediatric Infectious Diseases Journal* 12(12):973-975, December 1993.
7. Carlin SA et al., “Host Factors and Early Therapeutic Response in Acute Otitis Media” *The Journal of Pediatrics* 118(2):178-183, February 1991.