



Augmentin ES Advisory Committee Briefing Document

SB Document Number: BRL-025000/RSD-101GJ5/2

Table of Contents

List of Tables.....	000003
List of Figures.....	000004
Executive Summary.....	000005
1 Rationale for development of Augmentin ES.....	000008
1.1 Increasing incidence of antimicrobial resistance in <i>S. pneumoniae</i>	000008
1.2 In vitro Activity of Amoxicillin/clavulanic acid against <i>S. pneumoniae</i>	000009
1.2.1 Amoxicillin/clavulanic acid breakpoints for <i>S. pneumoniae</i>	000009
1.2.2 Recent surveillance data.....	000010
1.3 Clinical concerns.....	000013
1.4 Pharmacokinetic/pharmacodynamic rationale for Augmentin ES.....	000013
2 Clinical Summary.....	000017
2.1 Efficacy Summary.....	000018
2.2 Issues Raised by the Agency.....	000023
2.2.1 Bacteriological Response as the Primary Predictor of Efficacy in AOM.....	000023
2.2.2 Appropriate Timing for Assessment of Clinical Response.....	000025
2.2.3 Clinical Efficacy of Augmentin ES in AOM due to PRSP.....	000026
2.2.4 Overall Effectiveness of Augmentin ES in AOM due to PRSP.....	000029
2.3 Safety Summary.....	000031
3 Breakpoint Rationale.....	000033
3.1 Pharmacokinetics.....	000033
3.2 Pharmacodynamics.....	000037
3.3 Efficacy of amoxicillin/clavulanate against experimental respiratory tract infections caused by <i>S. pneumoniae</i>	000038
3.4 Efficacy in Support of Breakpoint.....	000038
3.5 Breakpoint Conclusion.....	000044
4 Overall Conclusions.....	000046
5 References.....	000047
Publications.....	000053

List of Tables

Table 1 Activity of amoxicillin/clavulanic acid and comparators against <i>S. pneumoniae</i> collected in the US in 1999	000011
Table 2 Activity of amoxicillin/clavulanic acid and comparators against penicillin-resistant <i>S. pneumoniae</i> collected in the US in 1999	000012
Table 3 Bacteriological Response by Baseline <i>S. pneumoniae</i> Susceptibility to Penicillin (PP and ITT Bacteriology Population) - On Therapy	000019
Table 4 Clinical Response at End of Therapy for <i>S. pneumoniae</i> Overall and by Penicillin MICs (PP/ITT Clinical Population)	000021
Table 5 Clinical Response at End of Therapy Visit by Baseline Pathogen (PP/ITT Clinical Population) - End of Therapy	000022
Table 6 Bacteriological Response On-Therapy and Clinical Response at End of Therapy (PP Populations) - Study 536	000030
Table 7 Pharmacokinetics (SD) of amoxicillin and clavulanic acid following administration of Augmentin ES to pediatric patients (n=18)	000036
Table 8 Activity of amoxicillin/clavulanate (14:1 dose) against penicillin-resistant <i>S. pneumoniae</i> in the rat RTI model	000038
Table 9 Bacteriological Response by Baseline <i>S. pneumoniae</i> Susceptibility to Amoxicillin/Clavulanic Acid (PP and ITT Bacteriology Population) - On-Therapy	000040
Table 10 Combined Analysis of On-Therapy Bacteriological Response in Patients with <i>S. pneumoniae</i> with Amoxicillin/Clavulanic Acid MICs = 4, 8 (PP and ITT Bacteriology Population)	000042
Table 11 Clinical Response by Baseline <i>S. pneumoniae</i> Susceptibility to Amoxicillin/Clavulanic Acid (PP Clinical Population at End of Therapy)	000043
Table 12 Combined Analysis of Clinical Response in Patients with <i>S. pneumoniae</i> with Amoxicillin/Clavulanic Acid MICs = 4, 8 (PP Clinical Population at End of Therapy)	000044
Table 13 Proposed amoxicillin/clavulanic acid breakpoints (mcg/mL) for Augmentin ES	000045

List of Figures

Figure 1 Incidence of penicillin-intermediate and penicillin-resistant <i>S. pneumoniae</i> in the US, 1979 - 1998	000008
Figure 2 In vivo efficacy versus time above amoxicillin MIC for <i>S. pneumoniae</i> in a neutropenic respiratory tract infection model	000015
Figure 3 Study Design	000018
Figure 4 Clinical Success Rates in AOM at End of Therapy (Per Protocol Populations) - Augmentin ES Study 536 and Comparator Clinical Studies	000026
Figure 5 Clinical Success Rates in AOM at Test of Cure (Per Protocol Populations) - Augmentin ES Study 536 and Comparator Clinical Studies	000028
Figure 6 Mean plasma concentration vs time profile of amoxicillin in children receiving 90/6.4mg/kg/day of amoxicillin/clavulanate in divided doses q12h, derived from the mean plasma concentration profile of amoxicillin obtained in 5 children receiving 45/6.4mg/kg/day of amoxicillin/clavulanate in divided doses q12h . . .	000034
Figure 7 Mean plasma concentration vs time profile of amoxicillin in children receiving 90/6.4mg/kg/day of amoxicillin/clavulanate in divided doses q12h	000035
Figure 8 Mean amoxicillin plasma-concentration profile following administration of Augmentin 600 suspension (45/3.2 mg/kg) to paediatric patients (n=18)	000037

Executive Summary

The incidence of penicillin-resistant strains of *Streptococcus pneumoniae* (PRSPs) is increasing world-wide. Multiple drug-resistance is high among isolates of *S. pneumoniae* expressing penicillin resistance; for this reason these organisms may be termed drug-resistant *S. pneumoniae* (DRSP). As a consequence of the appearance of these resistant isolates, the efficacy of therapy with antibacterials such as the penicillins, cephalosporins and macrolides may be compromised. *Augmentin* ES (amoxicillin/clavulanate potassium 14:1 formulation) has been developed on the basis of a combination of pharmacokinetic/pharmacodynamic considerations, *in vivo* animal, *in vitro* and clinical data. This product is intended for the treatment of acute otitis media (AOM) caused by susceptible strains of *S. pneumoniae*, (including penicillin-resistant strains, MIC value for penicillin ≥ 2 mcg/mL) where beta-lactamase-producing strains of *H. influenzae* or *M. catarrhalis* have not been ruled out as an etiology.

This briefing document summarizes the efficacy of *Augmentin* ES in the treatment of AOM due to penicillin resistant *S. pneumoniae* (PRSP) and *S. pneumoniae* with elevated amoxicillin/clavulanic acid MICs, as noted in SB's study 25000/536 titled "An open-label Study to Demonstrate Bacteriologic Efficacy of *Augmentin* ES in the Treatment of AOM Due to *S. pneumoniae*". Additionally, pharmacokinetic parameters, pharmacodynamics of amoxicillin/clavulanic acid and *in vivo* animal data are presented.

Augmentin ES (amoxicillin/clavulanate potassium 14:1 ratio) is a pediatric suspension for dosing at 90 mg/kg/day (amoxicillin component), dosed q12h. The dose of clavulanate is unchanged from the currently marketed 7:1 formulation (also dosed q12h). The original application for this formulation consisted of studies evaluating the pharmacokinetic/pharmacodynamics of the 14:1 formulation (Study 25000/446), and the comparative safety of this 14:1 formulation vs. the 7:1 formulation (Study 25000/447) in children with AOM. In response to the FDA's request for a confirmatory efficacy study of this 14:1 formulation in children with AOM due to PRSP, Study 536 was designed in discussion with the Agency.

Study 536 employed a double tympanocentesis design for strict evaluation of bacteriological efficacy of *Augmentin* ES against *S. pneumoniae* (including PRSP) by virtue of a repeat tympanocentesis performed on-therapy. Tympanocentesis was performed on days 4 to 6, the timepoint at which the natural history of the bacteriological course of AOM had previously been evaluated by Howie and

colleagues. Their work showed that *S. pneumoniae* had a spontaneous eradication rate in middle ear fluid of approximately 20-30% between days 3 and 7. Further, more recent studies (by Marchant, Carlin, Chonmaitre, Khurana, Dagan and others) have utilized this timepoint to evaluate the efficacy of various antibiotics in the treatment of AOM. These studies have indeed shown both differences between various agents, and correlation between clinical improvement and successful bacteriological eradication of pathogens, on-therapy, from the middle ear fluid (MEF) confirming that *in vivo* bacteriological outcome (i.e., baseline and on-therapy tympanocentesis) is the most sensitive and specific method for establishing the efficacy of an antibacterial agent in this indication.

In Study 536 the primary efficacy endpoint was on-therapy bacteriological response; the key clinical assessment was performed 2-6 days after completion of the 10 day course of *Augmentin* ES. The Agency has questioned SB's use of the end of therapy (EOT) window for the key clinical endpoint in Study 536. This timepoint was chosen as the most representative of the true clinical efficacy of antimicrobials in the treatment of AOM. The natural history of AOM includes frequent recurrences in the traditional test of cure (TOC) window of up to 30 days, and hence, comparing bacteriological eradication (a more exact evaluation of efficacy) with TOC clinical rates would doubtless provide a less accurate comparison of the utility of this drug in the treatment of AOM. As such, most clinical trials have reported clinical efficacy at EOT. The appropriate timing for clinical assessment in AOM studies is specifically addressed in this document.

There were 521 patients who completed Study 536 before 05 November 1999, when an interim analysis on the success of treatment of AOM due to PRSP was performed and submitted to the FDA as the clinical support study for the *Augmentin* ES sNDA; investigators continued to enroll (142 additional patients) until 12 June 2000 to gain additional data for *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4.0 mcg/mL. A total of 41 PRSP were isolated on initial tympanocentesis in the interim (PRSP) analysis of patients completed through 05 November 1999. Thirty-three of these 41 were in the bacteriological PP population, representing approximately 26% of all *S. pneumoniae* that were isolated on initial tympanocentesis. The sponsor believes that this is a substantial number of evaluable cases which provide strong data demonstrating the efficacy of *Augmentin* ES in the treatment of AOM due to PRSP.

The Agency has also asked SB to address the discrepancy in clinical response rate from EOT to TOC that was noted in the PRSP subset, which was larger than that seen overall for *S. pneumoniae* infections. Data are presented herein to exhibit

that the results for this select subgroup are within commonly seen rates of success for the treatment of AOM. Additionally, the risk factors for recurrence of AOM are largely shared with the risks for PRSP colonization and infection, thereby leading those patients with PRSP to have a higher risk for recurrence of AOM, regardless of prior effective antibiotic therapy.

Finally, clinical trial data are presented that support the efficacy of *Augmentin* ES against *S. pneumoniae* with amoxicillin/clavulanic acid MICs of ≤ 4 mcg/mL; lesser efficacy was demonstrated against *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 8 mcg/mL. While the numbers of isolates are limited due to the difficulty in isolating such organisms in a clinical trial, they are supported by the PK/PD model upon which beta-lactam drug efficacy is predicted. This predicted efficacy has been clearly demonstrated in animal studies.

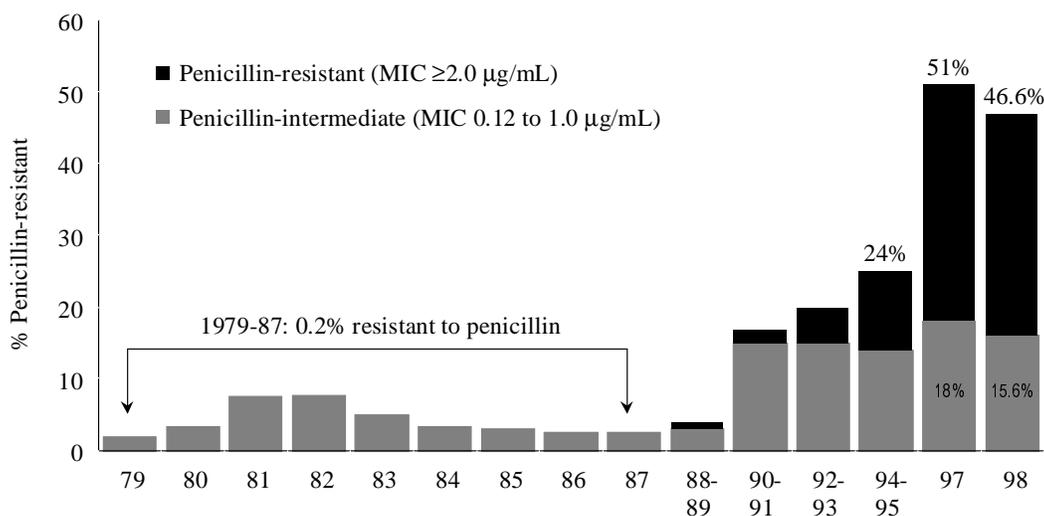
In summary, this document provides data that demonstrate the bacteriological and clinical efficacy of *Augmentin* ES, a 14:1 ratio product, in the treatment of AOM, including PRSP.

1 Rationale for development of Augmentin ES

1.1 Increasing incidence of antimicrobial resistance in *S. pneumoniae*

Infections caused by *Streptococcus pneumoniae* are responsible for significant morbidity and mortality in children and adults in the United States, accounting for an estimated 3,000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia [1] and approximately one third of the 30 million office visits for otitis media annually [2]. Penicillin has been the mainstay of treatment of pneumococcal infections for nearly 50 years and pneumococci have been considered routinely susceptible to penicillin (minimum inhibitory concentration (MIC) ≤ 0.06 mcg/mL). However, the incidence of penicillin-resistant *S. pneumoniae* has been increasing since the first confirmed clinical case was identified in Australia in 1967 [3]. Surveillance data have shown that the incidence of *S. pneumoniae* in the US that are non-susceptible to penicillin increased from below 10% in the late 1980s to greater than 50% in one study in 1997, with 33% of these isolates demonstrating resistance to penicillin (MIC ≥ 2 mcg/mL) (Figure 1) [4][5][6]. Penicillin resistance appears to be highest in the south eastern states of the U.S., with rates of penicillin non-susceptible isolates between 34% and 44% reported in recent studies [7][19].

Figure 1 Incidence of penicillin-intermediate and penicillin-resistant *S. pneumoniae* in the US, 1979 - 1998



1.2 *In vitro* Activity of Amoxicillin/clavulanic acid against *S. pneumoniae*

1.2.1 Amoxicillin/clavulanic acid breakpoints for *S. pneumoniae*

Prior to 1995 the *in vitro* activity of beta-lactam agents, including amoxicillin/clavulanic acid, against *S. pneumoniae* was predicted based on penicillin or ampicillin results. Isolates which were susceptible to penicillin or ampicillin, were considered susceptible to amoxicillin ± clavulanic acid. However, with the high levels of amoxicillin reached with standard oral dosing, it became apparent that, with the increasing incidence of PRSP, penicillin and ampicillin could no longer be used to predict the efficacy of amoxicillin ± clavulanic acid in respiratory tract infections. In 1996, the NCCLS and FDA granted new susceptibility testing breakpoints for amoxicillin ± clavulanic acid against *S. pneumoniae* based on *in vitro*, pharmacokinetic, animal and clinical data. The pharmacokinetic data presented focused on peak serum levels. The approved breakpoints were as follows: ≤0.5 mcg/mL susceptible, 1.0 mcg/mL intermediate and ≥2 mcg/mL resistant. (Note, amoxicillin/clavulanic acid is tested in a 2:1 ratio of amoxicillin:clavulanic acid; in this document, MICs are expressed in terms of the amoxicillin concentration, unless otherwise noted).

Since 1995, the pharmacokinetic/pharmacodynamic (PK/PD) parameter of time above MIC (T>MIC), not the peak serum concentration, has gained acceptance as the best predictor of clinical efficacy for beta-lactams. At the January 1998 NCCLS meeting, use of pharmacodynamic parameters was presented by Dr. William Craig as a meaningful criterion for assigning breakpoints for oral beta-lactams when testing *S. pneumoniae*. Craig and others found that a T>MIC of 40 – 50% of the dosing interval correlated with clinical efficacy for beta-lactams [21]. Results of PK/PD studies in animals demonstrated that killing of *S. pneumoniae* was observed for amoxicillin/clavulanic acid when the T>MIC was as low as 30%. Pharmaceutical companies were requested to present data to the NCCLS addressing this proposal. At the June 1998 NCCLS meeting, SB presented data which demonstrated that standard doses of amoxicillin ± clavulanic acid were sufficient to provide a T>MIC of ≥40% for *S. pneumoniae* with amoxicillin ± clavulanic acid MIC of ≤2 mcg/mL. Extensive *in vivo* PK/PD and efficacy studies, including bacteriological data from a clinical study in acute otitis media supported the susceptible breakpoint of ≤2 mcg/mL for amoxicillin/clavulanic acid, and this was approved by the NCCLS. In July 1998, a labeling supplement providing for the inclusion of this revised breakpoint on the Augmentin prescribing information was submitted to the agency and is currently pending.

Section 3 of this summary presents the rationale for the proposed breakpoint of ≤ 4 mcg/mL for *Augmentin* ES. The *in vitro* data in this section are presented using both the ≤ 2 mcg/mL (for the current formulations), and the ≤ 4 mcg/mL (for *Augmentin* ES) breakpoints.

1.2.2 Recent surveillance data

Recent surveillance studies have demonstrated a dramatic decrease in the susceptibility of *S. pneumoniae* to currently available antimicrobials. Data comparing the activity of amoxicillin/clavulanic acid and other agents against isolates collected in the US in 1999 [data on file] are presented in this section. The data are from the Alexander Project [53], an ongoing, multicenter, international surveillance study of community-acquired respiratory tract pathogens. A total of 1,462 *S. pneumoniae* isolates were collected in the US in 1999 and testing was conducted at Hershey Medical Center, Hershey, Pa, USA (Peter Appelbaum, M.D., Ph.D.) and Case Western Reserve University, Cleveland, Oh, USA (Michael Jacobs, M.D., Ph.D.).

A summary of the data is presented in Table 1. Of 1,462 isolates tested, only 52.1% were susceptible to penicillin. This was lower (46.3%) when the data for the pediatric (<12 years) isolates were analyzed separately. The isolates also demonstrated reduced susceptibility to the cephalosporins (39.0% to 60.4% of pediatric isolates susceptible); the macrolides (54.2% to 54.5% of pediatric isolates susceptible); and trimethoprim/ sulfamethoxazole (45.5% of pediatric isolates susceptible). At the current NCCLS-approved susceptible breakpoint, 85.9% of all isolates, and 81.7% of pediatric isolates were susceptible to amoxicillin/clavulanic acid. At the proposed susceptible breakpoint of ≤ 4 mcg/mL for the ES suspension, 90.8% of all isolates and 87.7% of pediatric isolates were susceptible to amoxicillin/clavulanic acid. The only agent to demonstrate similar activity was clindamycin, with 90.2% of pediatric isolates susceptible. However, clindamycin is not recommended for empiric use in AOM due to a lack of activity against *H. influenzae* and *M. catarrhalis* [16]. The quinolones were excluded because they are not indicated for use in pediatric patients.

Table 1 Activity of amoxicillin/clavulanic acid and comparators against *S. pneumoniae* collected in the US in 1999

Agent	All isolates (n=1462)		Pediatric isolates (n=661)	
	MIC90 (mcg/mL)	%Susceptible ^a	MIC90 (mcg/mL)	%Susceptible ^a
Amox/clav ^b	4	85.9 ^c , 90.8 ^d	8	81.7 ^c , 87.7 ^d
Penicillin	4	52.1	4	46.3
Cefaclor	≥32	43.0	≥32	39.0
Ceftriaxone	1	67.3	1	60.4
Cefuroxime	8	59.5	8	52.8
Azithromycin	≥32	60.3	≥32	54.2
Clarithromycin	16	60.7	16	54.5
Clindamycin	0.25	90.0	0.12	90.2
Doxycycline	8	na ^e	8	na ^e
TMP/SMX ^f	8	51.6	8	45.5

^aAccording to NCCLS breakpoints, M100-S10, January 2000

^bAmoxicillin/clavulanic acid, tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin content

^cPercent susceptible determined at ≤2 mcg/mL

^dPercent susceptible determined at ≤4 mcg/mL

^eNo NCCLS breakpoints available

^fTrimethoprim/sulfamethoxazole, tested at a 1:19 ratio; MICs are expressed in terms of the trimethoprim content

A summary of the activity of amoxicillin/clavulanic acid and comparators against penicillin-resistant *S. pneumoniae* is presented in Table 2. Aside from clindamycin, the most active agent was amoxicillin/clavulanic acid, with 70.9% of pediatric isolates susceptible at the proposed breakpoint of ≤ 4 mcg/mL for *Augmentin* ES. Only 14% or less of the PRSP pediatric isolates were susceptible to the cephalosporins, macrolides or trimethoprim/sulfamethoxazole.

Table 2 Activity of amoxicillin/clavulanic acid and comparators against penicillin-resistant *S. pneumoniae* collected in the US in 1999

Agent	All isolates (n=526)		Pediatric isolates (n=278)	
	MIC90 (mcg/mL)	%Susceptible ^a	MIC90 (mcg/mL)	%Susceptible ^a
Amox/clav ^b	8	61.2 ^c , 74.3 ^d	8	57.2 ^c , 70.9 ^d
Penicillin	4	0	4	0
Cefaclor	≥32	0	≥32	0
Ceftriaxone	2	11.4	2	7.5
Cefuroxime	8	0	16	0
Azithromycin	≥32	19.6	≥32	13.7
Clarithromycin	≥32	20.0	≥32	14.0
Clindamycin	≥4	78.5	≥4	78.8
Doxycycline	8	na ^e	8	na ^e
TMP/SMX ^f	≥16	8.2	≥16	6.1

^aAccording to NCCLS breakpoints, M100-S10, January 2000

^bAmoxicillin/clavulanic acid, tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin content

^cPercent susceptible determined at ≤2 mcg/mL

^dPercent susceptible determined at ≤4 mcg/mL

^eNo NCCLS breakpoints available

^fTrimethoprim/sulfamethoxazole, tested at a 1:19 ratio; MICs are expressed in terms of the trimethoprim content

In summary, the data presented clearly demonstrate that in the US, there is a high rate of resistance to currently available antimicrobials in *S. pneumoniae*, and this is particularly pronounced in isolates from pediatric patients. Only 46.3% of *S. pneumoniae* isolates from pediatric patients were susceptible to penicillin, and between 39% to 60% were susceptible to the cephalosporins, macrolides and trimethoprim/ sulfamethoxazole. At the proposed susceptible breakpoint of ≤4 mcg/mL for *Augmentin* ES, 87.7% of isolates were susceptible to amoxicillin/clavulanic acid. When the data for PRSP are analysed separately, the need for an agent with improved PK/PD is apparent. Only 14% or less of the PRSP isolates were susceptible to the cephalosporins, macrolides or

trimethoprim/sulfamethoxazole. At the proposed breakpoint of ≤ 4 mcg/mL for *Augmentin* ES, 70.9% of these isolates were susceptible to amoxicillin/clavulanic acid.

1.3 Clinical concerns

Antimicrobial therapy has important benefits in the management of acute otitis media (AOM), despite the high rate of spontaneous clinical recovery without treatment [30]. Antibiotics are given to specifically eradicate bacteria with the intent of both avoiding serious complications (mastoiditis, bacteremia, meningitis and auditory sequelae) and to decrease the duration and severity of symptoms [15][17][31]. *S. pneumoniae* is one of the most common bacterial causes of AOM and is the least likely to spontaneously resolve [16].

Penicillin-resistant *S. pneumoniae* (PRSP) are of added clinical concern because PRSP tend to be more resistant to multiple classes of antimicrobials than penicillin-susceptible strains. PRSP is now an established cause of AOM in Europe and the US [8][9], and reports of clinical failures in PRSP infections continue to be published, including failures in patients treated with antibiotics other than a penicillin [10][11]. Dagan, *et al*, reported both bacteriological and clinical failures in children with Acute Otitis Media treated with cephalosporin and azalide/macrolide agents in a series of clinical trials [12][13][14]. The quinolones are the most active agents against *S. pneumoniae* and resistance to quinolones is rare. However, as yet, the quinolones are not approved for use in pediatric patients. It is clear that there is a need for a safe and effective therapy for treatment of infections due to these multi-resistant strains.

1.4 Pharmacokinetic/pharmacodynamic rationale for Augmentin ES

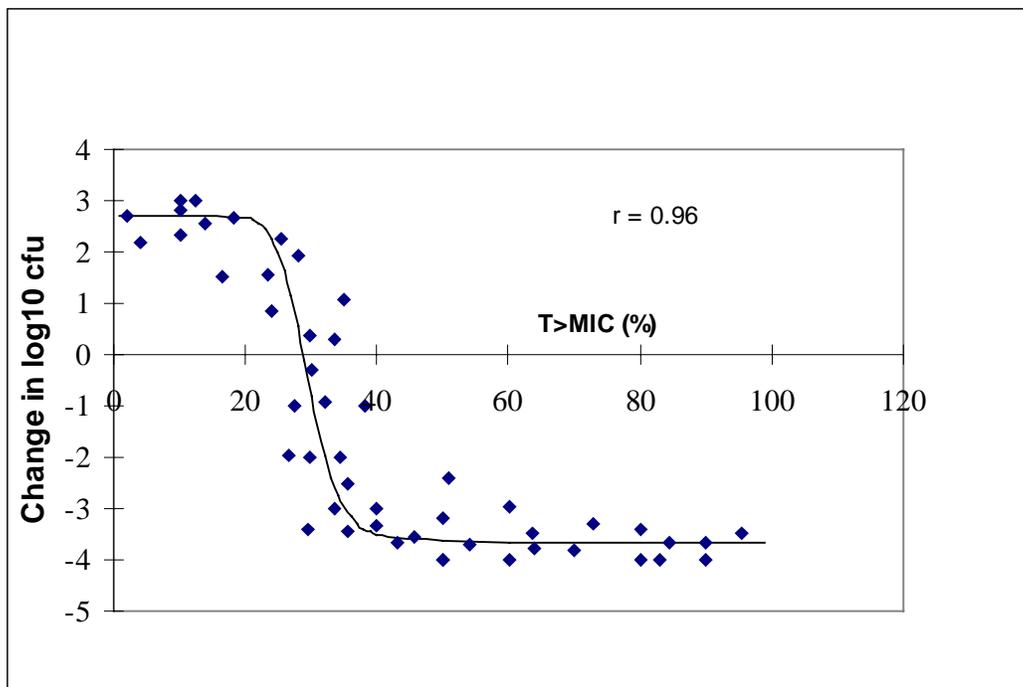
Currently, there is evidence that amoxicillin, with or without clavulanate, has the lowest MICs for *S. pneumoniae* among the available oral beta-lactam agents [5]. Further, the medical community has been proposing the use of higher doses of beta-lactam antibiotics as a reasonable approach to the challenge of treating infections that may involve resistant bacteria [16][17][18]. Barry *et al*. [20] have shown in an animal model of otitis media infection that moderately increased doses of amoxicillin were effective in treating infections due to penicillin resistant pneumococci. To determine if any proposed increase in dosage of antibiotic will

be clinically effective it is important to consider the pharmacokinetics and pharmacodynamics of the drug.

It has been determined that the time for which the serum concentrations exceeds the MIC ($T > MIC$) is the primary determinant of efficacy for beta-lactams. Data obtained from experimental thigh and respiratory infections suggest that for both Gram-positive and Gram-negative organisms, bacterial killing for cephalosporins occurs when serum concentrations exceed the MIC for 40% of the dosing interval, whilst for penicillins this is reduced to near 30% [21]. Recently Craig and Andes [8] in a review of bacteriologic efficacy data from a number of otitis media clinical trials demonstrated that there is a significant correlation between the time for which beta-lactam antibiotic concentrations in serum were above the MIC and efficacy in otitis media. Drusano and Craig showed that an 85 to 100% bacteriological cure rate was obtained when the $T > MIC$ was 40% or higher [21].

These data were confirmed in a study using a neutropenic mouse pneumonia model to assess the activity of amoxicillin against six strains of *S. pneumoniae* with MICs ranging from 0.01 to 4 mcg/mL [29]. In this study, when $T > MIC$ exceeded 40% the decrease in bacterial numbers was maximal and efficacy correlated directly with $T > MIC$ irrespective of the dosing interval. However, there was no significant decrease in numbers at $T > MIC$ of 25% or less of the dosing period (Figure 2).

Figure 2 In vivo efficacy versus time above amoxicillin MIC for *S. pneumoniae* in a neutropenic respiratory tract infection model



The most commonly prescribed pediatric formulation of Augmentin is a 7:1 ratio product, dosed at 45/6.4 mg/kg/day in divided doses q12h. This dose provides a mean T>MIC of approximately 41% for an amoxicillin MIC of 2 mcg/mL, and 28% for an amoxicillin MIC of 4 mcg/mL. *Augmentin* ES, containing a 14:1 ratio of amoxicillin/clavulanate, is designed to be dosed at 90/6.4 mg/kg/day in divided doses q12h. It was found that doubling the amount of amoxicillin provides a mean T>MIC of 46% for an amoxicillin MIC of 4 mcg/mL [49].

To determine if Augmentin ES was efficacious *in vivo*, an animal study was undertaken to examine the efficacy of the proposed 14:1 dose of amoxicillin/clavulanate against strains of *S. pneumoniae* exhibiting decreased susceptibility to amoxicillin [27]. Amoxicillin/clavulanate was administered to simulate concentrations obtained in pediatric patients following administration of either 22.5/3.2 mg/kg amoxicillin/clavulanate bid or 45/3.2 mg/kg amoxicillin/clavulanate bid. Amoxicillin/clavulanate at both dose levels reduced the number of viable bacteria in the lungs of animals infected with strains of *S. pneumoniae* with an amoxicillin MIC of 2 mcg/mL significantly ($p < 0.01$) compared with control animals. However, amoxicillin/clavulanate at the higher dose of 45/3.2 mg/kg was significantly more effective than the lower dose

(22.5/3.2 mg/kg) against *S. pneumoniae* strains with an amoxicillin MIC of 4 mcg/mL ($p < 0.01$).

These PK/PD data, including the *in vivo* animal efficacy study, provide evidence that predicts that Augmentin ES will be effective in treating infections due to *S. pneumoniae*.

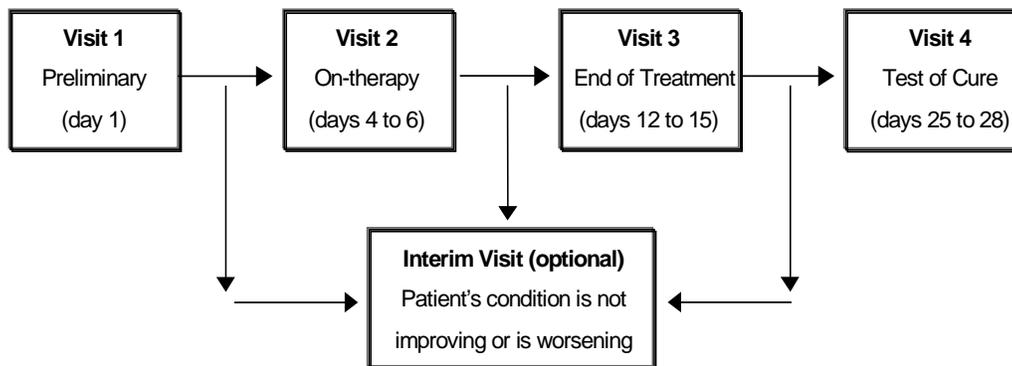
In summary, the continued decrease in susceptibility of *S. pneumoniae* isolates to currently available antimicrobials, in particular those for treating infections in pediatric patients, has created a need for a more effective agent. It has been proposed that increasing the dose of a currently available agent with a recognized safety profile will address that need. Pharmacokinetic studies have demonstrated that a 14:1 ratio of amoxicillin/clavulanate, dosed at 45 mg/kg (amoxicillin component) q12h (Augmentin ES) provides a T>MIC of 46% for an amoxicillin MIC of 4 mcg/mL [49], and this dose has demonstrated efficacy in an animal model of respiratory tract infection. Augmentin ES has therefore been developed for the treatment of acute otitis media caused by *S. pneumoniae* (including penicillin-resistant strains) and by beta-lactamase producing *H. influenzae* or *M. catarrhalis*.

2 Clinical Summary

Per agreement with the Agency, the sponsor sought a method of evaluating bacteriological efficacy of the *Augmentin* ES formulation, having confirmed its safety in Study 25000/447, titled: "A comparison of the safety and efficacy of q 12 hrs Augmentin-90/6.4 mg/kg/day and q 12 hrs Augmentin-45/6.4 mg/kg/day in the treatment of acute otitis media in children: A randomized double-blind, multicenter, comparative study." To achieve this goal, SmithKline Beecham sponsored Study 25000/536, titled: "An open-label study to demonstrate bacteriologic efficacy of *Augmentin* ES in the treatment of AOM due to *S. pneumoniae*." The study design and objectives, including the primary efficacy endpoint of on-therapy bacteriological response, were discussed with the Agency. In this study, bacteriological success was achieved in 122/125 (97.6%) of patients with *S. pneumoniae*, and in 31/33 (93.9%) of the penicillin-resistant *S. pneumoniae* that were isolated from the middle ear fluid of children with AOM (PP bacteriological population). Clinical success in the PRSP-PP population at end of therapy was also high (82.4%, 28/34).

The purpose of this pediatric AOM study was to identify, by tympanocentesis, patients with isolates of *S. pneumoniae* with amoxicillin/clavulanic acid MIC of 4.0 mcg/mL and isolates of *S. pneumoniae* with penicillin MICs of ≥ 2.0 mcg/mL, in order to determine the efficacy of treatment with amoxicillin/clavulanate at doses of 90/6.4 mg/kg/day for 10 days in children with AOM due to resistant *S. pneumoniae*. Tympanocentesis was performed at baseline and repeated at the on-therapy visit (day 4-6) in patients from whom *S. pneumoniae* had been isolated, and in all clinical failures, regardless of the initial pathogen isolated, at the time of failure. Additionally, some investigators repeated tympanocentesis in all enrollees (who grew a pathogen on initial tympanocentesis) at the on-therapy visit, day 4-6.

Patients were monitored clinically with an on-therapy visit (day 4-6), returned for an end-of-treatment visit (scheduled for day 12-15), and a test-of-cure visit (anytime after EOT if patient was a failure, otherwise day 25-28). An interim visit was mandated within 24 hours for all patients who contacted the investigator to report lack of clinical improvement or clinical worsening.

Figure 3 Study Design

As of 05 November 1999, it was deemed that a sufficient number of patients had been enrolled for the PRSP analysis. An efficacy summary of patients with AOM due to *S. pneumoniae* with penicillin MICs ≥ 2 mcg/mL who completed the study as of 05 November 1999 is presented here. Investigators were directed to continue to enroll patients into the clinical trial after 05 November 1999, the clinical cut-off for the PRSP analysis, in an effort to reach the proposed goal of 14 evaluable patients with AOM due to *S. pneumoniae* isolates with an amoxicillin/clavulanic acid MIC ≥ 4.0 mcg/mL. Section 3.4 of this document, Efficacy in Support of Breakpoint, contains an efficacy summary for these patients.

2.1 Efficacy Summary

The bacteriological intent-to-treat (ITT) population included all patients who took one dose of study medication and had a tympanocentesis at entry from which an initial pathogen had been isolated.

To be included in the per protocol (PP) bacteriological *S. pneumoniae* population, a patient had to have received at least three full days (6 doses) of study medication and have met all of the entry criteria. The patient must also have had a baseline MEF culture positive for *S. pneumoniae* (alone or with other pathogens) with a penicillin MIC ≥ 2 mcg/mL to meet the primary efficacy criteria. All patients with *S. pneumoniae* were to undergo a second tympanocentesis at days 4-6. The most frequent reasons for exclusion from the PP bacteriological *S. pneumoniae* population were that the patient did not have an on therapy visit on day 4-6 or received less than 3 days of study medication, the patient did not have 80-120% study medication compliance through the day 4-6 visit or that the patient received a prohibited medication prior to or during the on

therapy phase of the study. All references to patients with *S. pneumoniae* throughout this efficacy summary represent patients with *S. pneumoniae* alone or with other pathogens.

Bacteriological Response On-Therapy by Baseline Susceptibility to Penicillin

As discussed previously with the Agency, the primary endpoint was bacteriologic eradication at the on-therapy visit (day 4-6) of *S. pneumoniae*, including PRSP, from the MEF of children ages 3-48 months, who had AOM. The success rates, defined as eradication on repeat tympanocentesis, for both the PP and ITT populations, are presented in Table 3.

Table 3 Bacteriological Response by Baseline *S. pneumoniae* Susceptibility to Penicillin (PP and ITT Bacteriology Population) - On Therapy

		<i>Augmentin ES</i>			
		PP Bacteriological Population			
		Success		Failure	
Bacteriological Response		n/N	(%)	n/N	(%)
<i>S. pneumoniae</i>					
Penicillin MIC, mcg/mL					
Susceptible	≤ 0.06	63/64	(98.4)	1/64	(1.6)
Intermediate	≥ 0.12 to ≤ 1.0	22/22	(100.0)	0	
Resistant	≥ 2 mcg/mL	31/33	(93.9)	2/33	(6.1)
		ITT Bacteriological Population			
		Success		Failure	
Bacteriological Response		n/N	(%)	n/N	(%)
<i>S. pneumoniae</i>					
Penicillin MIC, mcg/mL					
Susceptible	≤ 0.06	77/81	(95.1)	4/81	(4.9)
Intermediate	≥ 0.12 to ≤ 1.0	27/30	(90.0)	3/30	(10.0)
Resistant	≥ 2	38/41	(92.7)	3/41	(7.3)

Note: 6 patients in the bacteriological PP and 7 in the bacteriological ITT population are missing penicillin MICs. They are counted as missing when displayed by MIC and are thus not included in tabulations by MIC.

As shown in Table 3, *Augmentin ES* demonstrated high bacteriological success rates against *S. pneumoniae*, including PRSP, in patients with AOM.

Clinical Response at End of Therapy

Secondary efficacy variables included the clinical response at end of therapy in patients infected with *S. pneumoniae*, with emphasis on isolates with penicillin MICs ≥ 2.0 mcg/mL and < 2.0 mcg/mL. Clinical response in patients with

S. pneumoniae isolates with amoxicillin/clavulanic MICs ≥ 4.0 mcg/mL and < 4.0 mcg/mL is presented in Section 3.4, Efficacy in Support of Breakpoint.

The clinical ITT population included all patients who took at least one dose of study medication. To be included in the PP clinical population at end of treatment, a patient must have received study medication and have had both baseline and end of treatment clinical assessments, though no one was excluded at EOT regardless of when they came in. A patient must also have had a baseline MEF culture positive for one or more of: *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus* or *S. pneumoniae*.

Table 4 presents clinical response at end of therapy in patients infected with *S. pneumoniae*, including isolates with penicillin MICs ≥ 2.0 mcg/mL and with penicillin MICs < 2.0 mcg/mL for the clinical PP/ITT populations at end of therapy. Clinical response at end of treatment was based upon the clinical outcome at end of treatment: clinical success (clinical cure or clinical improvement) or clinical failure.

In the clinical PP population at the end of therapy 89.3% (125/140) of patients with *S. pneumoniae* isolates were reported as clinical success. In patients with *S. pneumoniae* isolates with penicillin MICs of ≥ 2.0 mcg/mL, 82.4% (28/34) were reported as clinical success. In patients with *S. pneumoniae* isolates with penicillin MICs < 2.0 mcg/mL, 91.9% (91/99) were reported as clinical success.

In the clinical ITT population at the end of therapy 82.4% (131/159) of patients with *S. pneumoniae* isolates were reported as clinical success, 10.7% (17/159) were reported as failures and 6.9% (11/159) were missing clinical response at the end of therapy visit. There were 70.7% (29/41) of patients with *S. pneumoniae* isolates with penicillin MICs of ≥ 2.0 mcg/mL reported as clinical success, 14.6% (6/41) reported as clinical failures and 14.6% (6/41) were missing clinical assessments at the end of therapy. There were 86.5% (96/111) of patients with *S. pneumoniae* isolates with penicillin MICs < 2.0 mcg/mL reported as clinical success, 9.0% (10/111) reported as clinical failures and 4.5% (5/111) were missing clinical assessment at the end of therapy.

Table 4 Clinical Response at End of Therapy for *S. pneumoniae* Overall and by Penicillin MICs (PP/ITT Clinical Population)

Clinical Response at End of Therapy	<i>S. pneumoniae</i>		<i>Augmentin ES</i> <i>S. pneumoniae</i> with penicillin MICs \geq 2 mcg/mL		<i>S. pneumoniae</i> with penicillin MICs $<$ 2 mcg/mL	
	n/N	%	n/N	%	n/N	%
PP						
Success, n (%)	125/140	(89.3)	28/34	(82.4)	91/99	(91.9)
Failure, n (%)	15/140	(10.7)	6/34	(17.6)	8/99	(8.1)
ITT						
Success, n (%)	131/159	(82.4)	29/41	(70.7)	96/111	(86.5)
Failure, n (%)	17/159	(10.7)	6/41	(14.6)	10/111	(9.0)
Missing Clinical Response, n (%)	11/159	(6.9)	6/41	(14.6)	5/111	(4.5)

Note: In the clinical PP population 7 patients are missing penicillin MICs. They are counted as missing when displayed by MIC and are thus not included in tabulations by MIC.

Bacteriological and Clinical Response in Other Pathogens

The bacteriological and clinical response rates for other common bacterial pathogens, such as *H. influenzae* and *M. catarrhalis*, were comparable to *S. pneumoniae*. Beta-lactamase production was identified in 35.5% (70/197) of the *H. influenzae*, 100% (31/31) of *M. catarrhalis* and 91.7% (11/12) of *S. aureus* isolated in the ITT population.

Two groups were available for the analysis of bacteriological efficacy of *Augmentin ES* against pathogens other than *S. pneumoniae*: one group had a repeat tympanocentesis (confirmed bacteriological efficacy), while the other group had presumed bacteriological efficacy, based on their EOT clinical evaluation. The confirmed bacteriological eradication of *H. influenzae* in patients with repeat tympanocentesis was 92.6% (75/81). *M. catarrhalis* was successfully eradicated in 100% (11/11) of the PP patients. The rates of "presumed eradication" were slightly lower for these two organisms, 84.4% (54/64) and 88.9% (8/9), respectively, but are within commonly reported rates of clinical success in AOM [12][50].

These rates of bacteriological success, in light of the significant numbers of beta-lactamase producing bacteria, and the significant percentage of PRSP isolates, 27.7%, (33/119 of *S. pneumoniae* with a penicillin MIC reported in the bacteriology PP population) further demonstrate the utility of *Augmentin ES* in the treatment of AOM, including cases due to several types of resistant pathogens. The clinical responses for *H. influenzae*, *M. catarrhalis*, *S. aureus* and *S. pyogenes* were also supportive of the efficacy of *Augmentin ES* in the treatment

of AOM, with success rates ranging from 83.3% (10/12 *S. aureus*) to 92.9% (13/14 *S. pyogenes*) in the clinical PP population at EOT. The results were slightly lower for clinical response in the ITT clinical population at end of therapy (Table 5).

Table 5 Clinical Response at End of Therapy Visit by Baseline Pathogen (PP/ITT Clinical Population) - End of Therapy

<i>Augmentin ES</i>						
PP Clinical Response						
Pathogen	Success		Failure			
	n/N	(%)	n/N	(%)		
<i>H. influenzae</i>	141/162	(87.0)	21/162	(13.0)		
<i>M. catarrhalis</i>	22/26	(84.6)	4/26	(15.4)		
<i>S. pyogenes</i>	13/14	(92.9)	1/14	(7.1)		
<i>S. aureus</i>	10/12	(83.3)	2/12	(16.7)		
ITT Clinical Response						
Pathogen	n/N	Success		Failure		Missing
		(%)	n/N	(%)	(%)	
<i>H. influenzae</i>	151/197	(76.6)	27/197	(13.7)	19/197	(9.6)
<i>M. catarrhalis</i>	23/31	(74.2)	4/31	(12.9)	4/31	(12.9)
<i>S. pyogenes</i>	14/17	(82.4)	2/17	(11.8)	1/17	(5.9)
<i>S. aureus</i>	10/12	(83.3)	2/12	(16.7)	0	

As anticipated in the natural history of this disease, there were a moderate number of recurrences/reinfections in the clinical population after the end of therapy visit [38]. This is reflected in the lower clinical success rates at the test of cure visit. In the clinical PP population in patients with *S. pneumoniae* isolates with penicillin MICs of ≥ 2.0 mcg/mL, 52.9% (18/34) were reported as clinical success at the test of cure visit (day 25-28). In patients with *S. pneumoniae* isolates with penicillin MICs < 2.0 mcg/mL, 80.4% (78/97) were reported as clinical success. The clinical response of baseline pathogens in the clinical PP population at test of cure ranged from 60.0% (15/25) success for patients with *M. catarrhalis* isolated at baseline, 67.7% (107/158) success for patients with *H. influenzae* isolated at baseline, to 80.0% (12/15) clinical success in patients with *S. pyogenes* isolated at baseline. For comparison, no data has been published to date on recurrence rates within 28 days (TOC time-point) by *S. pneumoniae* susceptibility to penicillin. Experts have recommended evaluating the on-therapy bacteriological efficacy of antimicrobials in the treatment of AOM as the most sensitive time-point for comparing differences [43].

2.2 Issues Raised by the Agency

The Agency has raised an issue concerning the clinical benefit of *Augmentin* ES due to the lower clinical success rate in patients with AOM due to PRSP at the follow-up assessment (test of cure visit, study days 25-28). The Agency further asked for an explanation for the disparity in the clinical outcome at test of cure compared to the bacteriological results while the patient was on therapy. In the following sections, this concern is addressed by presenting the rationale that supports current standards for the assessment of antibacterial efficacy in AOM. This rationale identifies two key points for the appropriate determination of efficacy in AOM; first, that *in vivo* bacteriological outcome (ie, baseline and on-therapy tympanocentesis) is the most sensitive and specific method for establishing the efficacy of an antibacterial agent in this indication [47]; secondly, that the most accurate time for assessment of clinical response in AOM is the immediate period following completion of treatment.

This rationale supports the conclusion that the bacteriological and clinical efficacy for *Augmentin* ES in Study 536 adequately demonstrate the therapeutic benefit of *Augmentin* ES in the treatment of patients with AOM due to PRSP.

2.2.1 Bacteriological Response as the Primary Predictor of Efficacy in AOM

The Correlation of Bacteriological and Clinical Outcome

Establishing the efficacy of an antibacterial agent in AOM is complicated by factors other than the ability of the agent to eradicate pathogens from middle ear fluid (MEF). While in the majority of cases of AOM there is agreement between bacteriological and clinical outcome, in some situations there are differences. Some patients, for example, will eliminate pathogenic bacteria from the middle ear fluid by host defenses alone resulting in a high rate of spontaneous clinical recovery or symptomatic improvement in AOM without antibacterial therapy. Other patients will have persistent symptoms despite effective antibacterial therapy, for example, due to concurrent viral infection [47].

The impact of discrepancies between bacteriological and clinical outcome was studied by Marchant (1992) with respect to identifying optimum strategies for assessment of antibacterial agents in AOM [43]. The conclusion of this report was that if efficacy is measured by symptomatic response alone "drugs with excellent antibacterial activity will appear less efficacious than they really are and drugs with poor antibacterial activity will appear more efficacious than they really are". Furthermore, the authors suggest that the measurement of *in vivo*

bacteriological efficacy is a useful strategy to avoid the tendency towards false optimism i.e. a drug with poor antibacterial activity appearing clinically effective (termed the "Pollyanna Phenomenon") [43].

The studies conducted by Marchant demonstrated that early bacteriologic eradication is associated with high clinical success rates in infants and children treated with antibiotics for AOM [43]. Similarly Dagan (1998) demonstrated that clinical failure (defined as the need for additional antibiotic treatment during the first 10 days after initiation of treatment) was associated with the inability to eradicate the causative organisms from MEF within 3-4 days of initiation of therapy. This latter study also demonstrated that early eradication was associated with more rapid improvement in clinical symptoms [31].

In summary, bacteriological outcome is considered by experts in AOM treatment, to be a more convincing standard of efficacy than clinical outcome alone. Furthermore, bacteriological efficacy early on in treatment has also been established as a predictor of clinical efficacy in AOM and therefore provides a sensitive and specific method for establishing the efficacy of an antibacterial agent in this indication [31] [16] [43] [44] [48].

Implications for Clinical Trial Design

In clinical trials that aim to precisely define the efficacy of antibacterial agents against the pathogens implicated in AOM, bacteriological efficacy is best evaluated by tympanocentesis both before therapy and during therapy. The timing of the second tympanocentesis is generally considered best carried out 4-6 days after start of antibiotic therapy since at this point efficacy should be demonstrated if the agent is going to work. The day 4-6 timing for bacteriological evaluation is influenced by the IDSA guidelines which recommend clinical evaluation of AOM patients at Day 3-5, and the FDA Draft Guidance for Industry which notes that three days is a reasonable timepoint to re-evaluate, and a patient who is not improving may be considered a failure. Furthermore, repeat tympanocentesis later than Day 6 may have allowed inclusion of a sizable proportion of spontaneous resolution cases into the success category.

The non-comparative *Augmentin* ES study in AOM, Study 536, was designed to demonstrate a definitive bacteriologic cure in-line with current standards of research. The "double-tympanocentesis" technique was used so that bacteriologic cure was based on confirmed bacteriological eradication thus overcoming the so-called "Pollyanna effect". The confirmed bacteriologic eradication, via a repeat

tympanocentesis at Day 4-6, was the most precise evaluation that could be made to study the bacteriological efficacy of *Augmentin* ES.

2.2.2 Appropriate Timing for Assessment of Clinical Response

Early Recurrences in Acute Otitis Media

Following appropriate antibiotic treatment for an episode of AOM, early recurrences, defined as those occurring within one month of the initial diagnosis, can be encountered in up to one-third of cases [38][39]. It is well accepted that clinical recurrences during this period of time often represent a new infection (reinfection) rather than treatment failure of the initial pathogen. One study (Carlin *et al*) [38], for example, investigated the cause of early recurrence in 36 (35%) of 103 infants and children who had been treated for AOM. Of 29 children with repeat tympanocentesis, 13 (44.8%) had no pathogen recovered, 12 (41.4%) had a new infection and only 4 (13.8%) had a relapse with the same organism. Recent data from a large study of 1077 patients with AOM aged 3-36 months also confirms that new infection is the main of cause of clinical relapses of AOM within one month [40].

Implications for Clinical Study Design

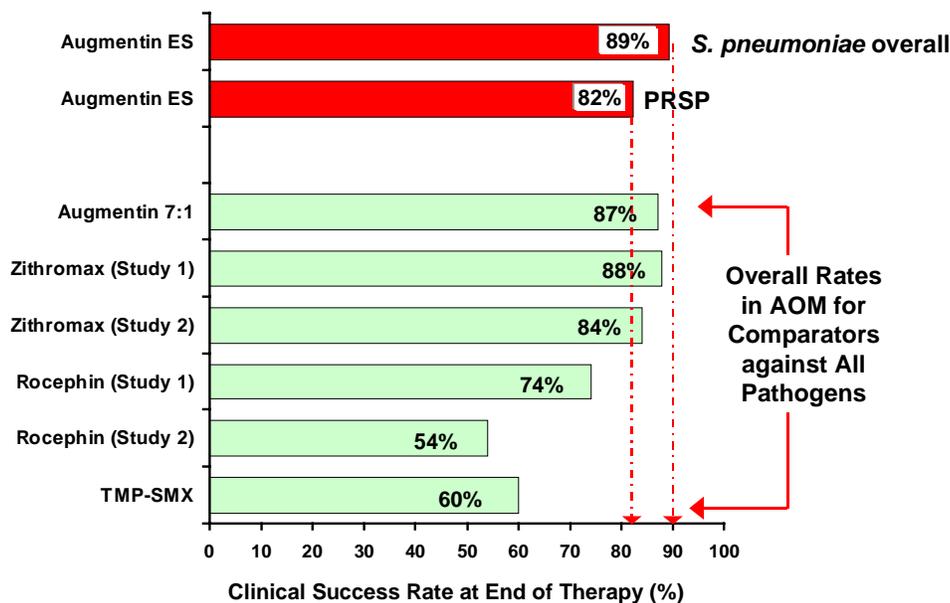
In AOM, the immediate period following completion of treatment is the most appropriate time for the accurate assessment of clinical response to an antibacterial agent [30]. Clinical assessment at this time avoids the confounding effect of the high recurrence rate due to new infections that predominates 2-3 weeks after the completion of treatment. Furthermore, early clinical response has been shown to correlate with the eradication of pathogens from middle ear fluid, which is agreed by experts as the most reliable predictor of treatment efficacy in AOM. In clinical trials designed to demonstrate the efficacy of antibacterial agents in children with AOM, the current standard for the principal assessment of clinical response is at end of therapy usually conducted between 1-4 days following completion of therapy [14][41][46].

Based on the clinical course of AOM as described above and the benchmark from recently published clinical studies in this indication [14][41][46], the main clinical endpoint in Study 536 was the end of therapy visit (Day 12-15) to be performed 2-5 days after completion of therapy and incorporating the period when most bacteriological relapses occur. The follow-up/TOC visit (Day 25-28) was to be between 2-3 weeks after the end of therapy, the period of time in which clinical infection most often represents infection with a new pathogen.

2.2.3 Clinical Efficacy of *Augmentin* ES in AOM due to PRSP

Augmentin ES demonstrated a high clinical success rate in the treatment of patients with acute otitis media due to PRSP (penicillin MIC ≥ 2 mcg/mL). The success rate of 82% (28/34) was only slightly less than the success rate in this study for AOM involving all *S. pneumoniae* (89%, 125/140). Furthermore, the PRSP success rate with *Augmentin* ES treatment was at least comparable to the overall rates of success in AOM (regardless of pathogen) reported in pivotal trials of approved antibacterial agents. In particular, compared with reported studies evaluating ceftriaxone (Rocephin), the PRSP success rate for *Augmentin* ES was noticeably higher than the clinical success rate reported for all pathogens in the ceftriaxone studies. The *Augmentin* ES and comparator success rates are compared in Figure 4.

Figure 4 Clinical Success Rates in AOM at End of Therapy (Per Protocol Populations) - *Augmentin* ES Study 536 and Comparator Clinical Studies



Note: comparator rates are taken from clinical trials of agents licensed for acute otitis media as reported in the product labelling

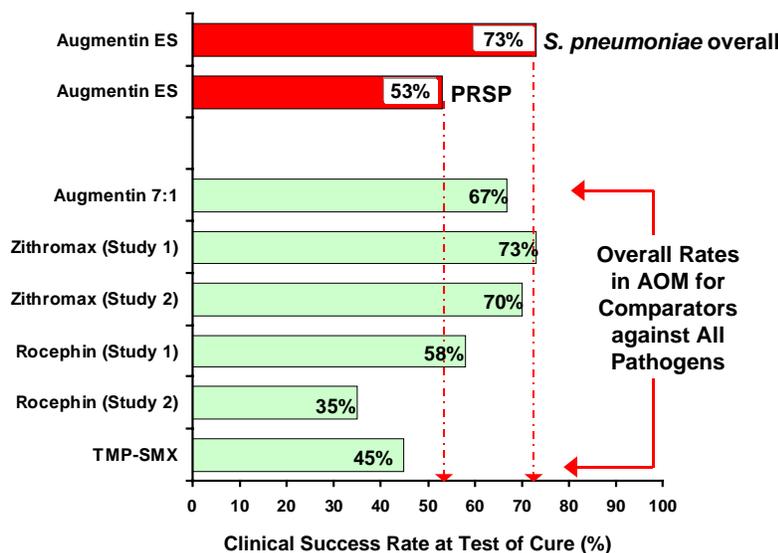
Since Study 536 is the first double tympanocentesis clinical trial specifically designed to determine the effectiveness of an antibacterial agent in AOM patients with PRSP, there are no adequate historical comparator data to allow an equal

comparison with the *Augmentin* ES PRSP clinical success rate¹. However, experts in the treatment of AOM recognize that there is an increased risk of treatment failure (clinical and bacteriologic) with commonly used oral antibiotic agents, when penicillin resistance, even at the intermediate level, is present in acute otitis media [34][35][36][37][13][42][12]. This increased risk of treatment failure highlights the clinical importance of the PRSP clinical success rate achieved with *Augmentin* ES which is comparable with the highest rates reported for *Augmentin* 7:1 and other comparator regimens in studies with more treatment-favorable populations.

The results of clinical response at the test of cure visit were reported for the completeness of the evaluation of Study 536, even though the efficacy of antibacterial agents is confounded by the high reinfection rate during this period of time [38][39][40]. Regardless of this, it is important to note that the clinical success rates in AOM due to *S. pneumoniae* overall (73%) which includes approximately 25% PRSP isolates, is at least as good as that for historical comparator agents due to any pathogen (range 35%-73%). Furthermore the clinical success for patients with PRSP (53%) is also within the overall success range in AOM for historical comparators (see Figure 5). In other words, the proportion of patients with isolates of *S. pneumoniae* with MICs ≥ 2 mcg/mL in Study 536 who remained clinical successes at test of cure, was similar to the reported success in all enrolled AOM patients in other trials who may have not had bacteriological confirmation of AOM, let alone highly resistant bacteria.

¹ The design of Study 536 was the subject of discussion between FDA and SB. The noncomparative design was agreed to be a reasonable approach considering implications for sample size and tympanocentesis requirements as well as the lack of an established or appropriate comparator for a comparative study. The 'double tympanocentesis' design allowed a definitive bacteriologic cure rate to be established in a noncomparative setting.

Figure 5 Clinical Success Rates in AOM at Test of Cure (Per Protocol Populations)
- Augmentin ES Study 536 and Comparator Clinical Studies



Note: comparator rates are taken from clinical trials of agents licensed for acute otitis media as reported in the product labelling

As cited previously, Carlin *et al*, reported a reinfection (with a new organism) rate of 41.4% when examining patients within a month of initial diagnosis [38]. It is thus likely that a number of failures reported at TOC in Study 536 actually represent a reinfection with a new organism, rather than a relapse due to failure of the initial antibiotic treatment. Applying the reinfection rate of 41.4% reported by Carlin *et al* to the data in Study 536, of 16 reported failures in the PRSP population, 7 patients may perhaps have been successfully treated, only to become reinfected with a new organism. Of the 19 reported failures in the non-PRSP population, 8 patients may perhaps have been successfully treated, only to become reinfected with a new organism. Thus the true success rate may be 74% (25/34) for PRSP, and 89% (86/97) for non-PRSP patients.

Protocol 536 called for a second tympanocentesis between days 4 to 6 for all patients from whom *S. pneumoniae* was isolated on initial tympanocentesis. Thus information on bacteriology at the TOC visit for patients with *S. pneumoniae* at baseline were not expected to be available. However, a review of the data shows that three repeat tympanocenteses were performed in the TOC window (specifically, one on day 21 and two on day 22) on 2 patients with *S. pneumoniae* at baseline. Pulsed-field gel electrophoresis (PFGE) was used to differentiate

between reinfection with new organisms and relapse with the same organism as at baseline. New infection was documented in 1/3 (33.3%) of infected ears. Similarly, 1/3 of patients with *H. influenzae* at baseline had documented new infection at test of cure. While these data are limited, they are supportive of the Carlin *et al*, data regarding rates of reinfection. These findings support the argument that assessment of clinical cure at TOC is confounded by reinfection.

The overall *S. pneumoniae* clinical success rates in Study 536 require further comment. The clinical success rate for *Augmentin* ES at both end of therapy and test of cure was at the top of the success range reported for other comparator agents frequently prescribed in AOM (Figures 1 and 2). However in Study 536, only those patients with proven bacterial AOM were included in the PP population and hence cases of viral and/or otitis media with effusion (OME) which could favorably influence the clinical results were not included, unlike studies with clinical response as the primary objective. Further, these results for Study 536 are only for the patients with *S. pneumoniae*, the organism which is least likely to resolve without the benefit of antimicrobial therapy [48][16][52]. The increasing prevalence of *S. pneumoniae* with elevated MICs, as illustrated by the approximate 25% incidence of isolates with MIC ≥ 2 mcg/mL in Study 536, also puts the historical comparator studies conducted some years ago at a favorable advantage.

2.2.4 Overall Effectiveness of *Augmentin* ES in AOM due to PRSP

In Study 536, the bacteriological success rate on-therapy (93.9%) and the clinical success rate at end of therapy (82.4%) for patients with AOM due to PRSP treated with *Augmentin* ES, are entirely consistent with an agent to be considered efficacious in this condition [43]. As summarized in Table 6, the responses for *Augmentin* ES in AOM due to PRSP differ only slightly to those for susceptible *S. pneumoniae* and those with intermediate susceptibility.

Table 6 Bacteriological Response On-Therapy and Clinical Response at End of Therapy (PP Populations) - Study 536

<i>S. pneumoniae</i> by Penicillin MIC		Bacteriological Response On-Therapy			
		Success		Failure	
PP Bacteriology Population		n/N	(%)	n/N	(%)
Overall <i>S. pneumoniae</i>		122/125	(97.6)	3/125	(2.4)
Susceptible	Penicillin MIC ≤ 0.06 mcg/mL	63/64	(98.4)	1/64	(1.6)
Intermediate	Penicillin MIC ≥ 0.12 to ≤ 1.0 mcg/mL	22/22	(100.0)	0	
Resistant	Penicillin MIC ≥ 2 mcg/mL	31/33	(93.9)	2/33	(6.1)

PP Clinical Population		Clinical Response at End of Therapy			
		Success		Failure	
Overall <i>S. pneumoniae</i>		125/140	(89.3)	15/140	(10.7)
Susceptible	Penicillin MIC ≤ 0.06 mcg/mL	68/74	(91.9)	6/74	(8.1)
Intermediate	Penicillin MIC ≥ 0.12 to ≤ 1.0 mcg/mL	23/25	(92.0)	2/25	(8.0)
Resistant	Penicillin MIC ≥ 2 mcg/mL	28/34	(82.4)	6/34	(17.6)

Although the clinical success rate at test of cure for *Augmentin* ES in AOM due to PRSP was within the range of successes reported for comparator agents in AOM overall, the discrepancy with on-therapy bacteriological response is likely attributable to the high infection rate with new bacterial species that occurs as part of the natural course of the disease [38][39]. Furthermore, the greater discrepancy at test of cure for PRSP (clinical success rate of 52.9%) versus penicillin sensitive (80%) or intermediate (83%) *S. pneumoniae*, may be due to a higher recurrence/reinfection rate in patients with PRSP, as it has been well-documented that several of the risk factors predisposing to PRSP (e.g., age <2 years, day care, etc) are identical to those predisposing to recurrent AOM [30]. Interestingly, patients with PRSP in Study 536, when compared retrospectively to patients with penicillin susceptible *S. pneumoniae*, were of a younger age (13.4 months vs 18.8 months; p-value = 0.0063), had more frequently received antibiotics in the last 3 months (77% vs 42%; p-value = 0.004) and had a higher incidence of a history of AOM (59% vs 36%; p-value = 0.027). Additionally, a higher proportion of patients with PRSP attended daycare (40.9% vs 35.8% for the penicillin susceptible *S. pneumoniae* group), although this difference was not found to be statistically significant (p-value = 0.804). Klein noted that younger children who had early onset of AOM, or recurrent AOM, tended to continue to have recurrent AOM, regardless of treatment. They tend to be a somewhat self-defined group [48]. In summary, the outcome at test of cure which is influenced by reinfection cannot accurately reflect the clinical efficacy of the drug in AOM. This is particularly critical to efficacy in patients with PRSP who are likely to be at greater risk for recurrent AOM.

In conclusion, the data from Study 536 support the bacterial eradication and symptomatic benefit of treatment with *Augmentin* ES for children with AOM due to PRSP. The bacteriological success rate on-therapy and the clinical success rate were sufficiently high to conclude that efficacy was demonstrated in this group of patients. These response measurements represent the most appropriate endpoints to determine the efficacy of an antibacterial agent in AOM.

2.3 Safety Summary

Evaluation of the safety of Study 536 demonstrates that *Augmentin* ES is well tolerated. The rate of serious adverse experiences (SAEs) reported was 1.3% (7/521), with only diarrhea (n=2) being reported in more than one patient. The rate of withdrawal due to AE was 4.6% (24/521), with the rate of withdrawal for diarrhea being reported as 2.9% (n=15).

The safety of *Augmentin* ES was previously established in SB protocol 25000/447. In this trial (25000/447), rates of protocol defined diarrhea (PDD) in the ITT bowel habit population were comparable at 11.1% (22/198) in the *Augmentin* 90/6.4 mg/kg/day formulation (Aug-90; ES) group and 9.4% (19/203) in the *Augmentin* 45/6.4 mg/kg/day formulation (Aug-45) group. In the current clinical study, 25000/536, the rate of PDD was again comparable at 12.5% (65/521).

Overall rates of AEs in these trials also establish that *Augmentin* ES has a safety profile that reflects the currently marketed *Augmentin* 45/6.4 mg/kg/day formulation. The rates of reported AEs in 25000/447 were 50.2% (Aug-90) and 47.3% (Aug-45)[51], while in the 25000/536 study, the rate was 38.8%. There were no deaths reported during either study.

In the combined adverse experience profiles from studies 25000/447 and 25000/536 safety was assessed in a total of 722 pediatric patients who received at least one dose of *Augmentin* ES in either study. Approximately 42% of patients reported at least one adverse experience. Fever (7.2%) was the most frequently reported adverse experience irrespective of relationship to study medication. In Study 536, since PDD was already being captured by diary card entries, sites were instructed not to record bowel habits as adverse experiences while on treatment (unless severe enough to withdraw the patient or if the diarrhea fulfilled the definition of an SAE); nevertheless, some investigators did record diarrhea as an AE.

Adverse experiences considered by the investigators to have either a probable or suspected relationship to study medication were reported by 13.3% of patients. Contact dermatitis (i.e., diaper rash), reported by 3.5% of patients, was the most frequently reported adverse experience with a probable or suspected relationship to *Augmentin* ES. Diarrhea, vomiting, moniliasis and rash were the only other adverse experiences with a probable or suspected relationship to study medication occurring in more than 1.0% of patients.

Thirty-two (4.4%) patients who participated in either study 25000/447 or 25000/536 were withdrawn for adverse experiences considered by the investigators to have a probable or suspected relationship to study medication. Diarrhea (2.5%) and vomiting (1.4%) were the most common "related" adverse experiences leading to withdrawal. All other related events leading to withdrawal were reported by less than 1.0% of patients.

3 Breakpoint Rationale

The following data are presented to support new breakpoints for amoxicillin/clavulanic acid for *S. pneumoniae* for the *Augmentin* ES formulation.

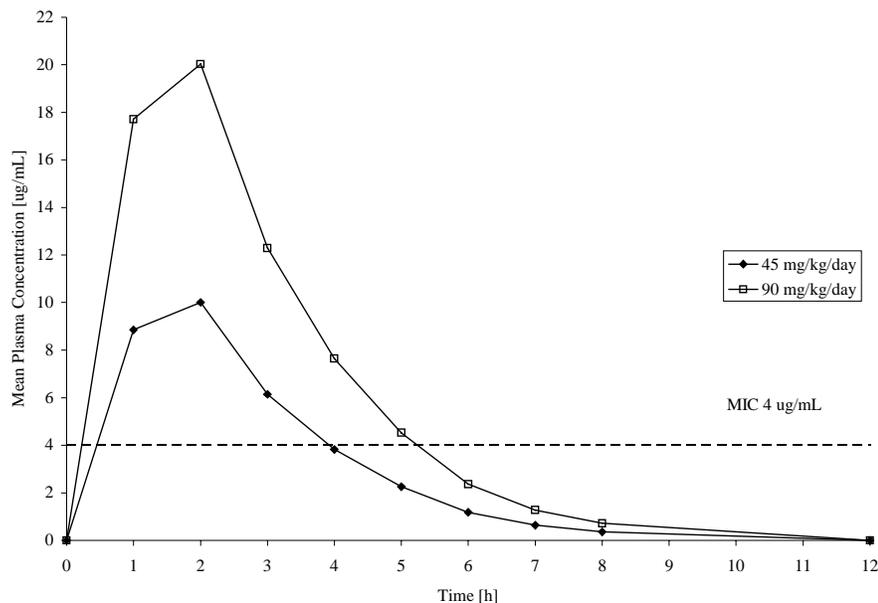
- Pharmacokinetic parameters
- Pharmacodynamics of amoxicillin/clavulanic acid
- *In vivo* animal data
- Clinical efficacy data

3.1 Pharmacokinetics

In the original application for the 14:1 *Augmentin* oral suspension (NDA 50-755; October 31, 1997) two studies were described in which pharmacokinetic data were obtained in pediatric subjects. The mean T>MIC value described below for study 25000/382 is based upon extrapolated plasma concentrations, and we believe that this approach is valid due to the linear pharmacokinetics of amoxicillin.

Study 25000/382 [23] was designed to evaluate the steady state pharmacokinetic profiles of amoxicillin and clavulanate in children aged one month to 12 years after receiving *Augmentin* 45/6.4 mg/kg/day in divided doses q12h, or 40/10 mg/kg/day in divided doses q8h for a total of 10 days. In the study, five subjects were administered *Augmentin* at 45/6.4 mg/kg/day in divided doses q12h. On the pharmacokinetic assessment day (no earlier than 48 hours after therapy was begun, and no later than nine days after start of therapy), blood samples were drawn at pre-dose, hourly up to eight hours, and at 12 h after the designated dose. In order to estimate the pharmacokinetics and T>MIC of amoxicillin that would have been achieved had the subjects given 45/6.4 mg/kg/day q12h actually received double the amoxicillin dose, i.e. 90/6.4 mg/kg/day in divided doses q 12h, their individual plasma concentration-time data were doubled on the basis of the known pharmacokinetic linearity of amoxicillin [24]. This principle has been depicted on mean data in Figure 6. The corresponding T>MIC values were then calculated from the new individual plasma concentration vs time profiles. Using this approach, it is estimated that a dose of 90/6.4 mg/kg/day q12h will result in a mean T>MIC of approximately 41% (4.9 h/ 12 h) of a dosing interval, for an amoxicillin MIC of 4 mcg/mL [8].

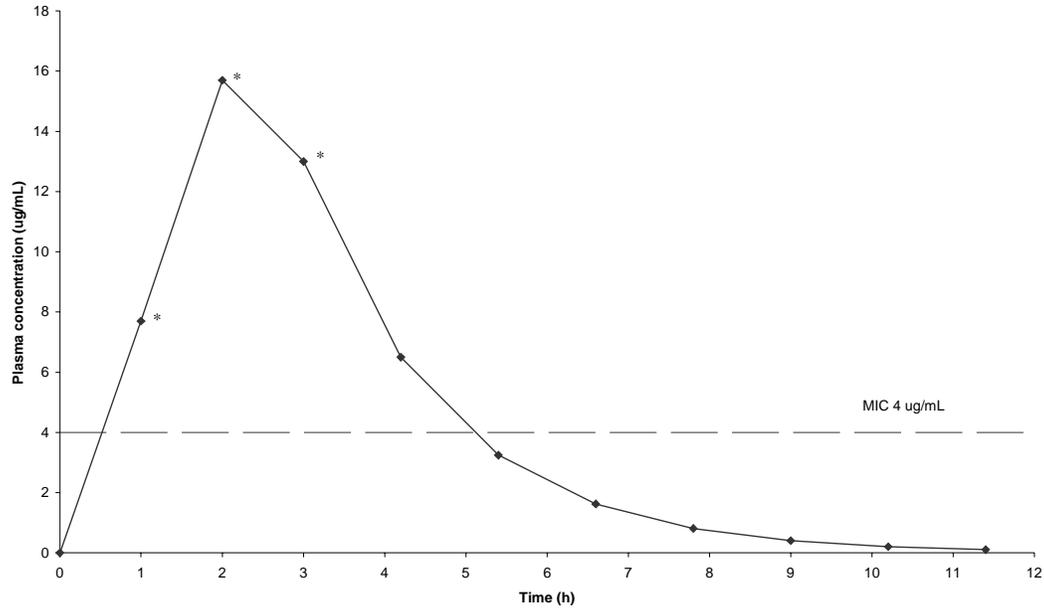
Figure 6 Mean plasma concentration vs time profile of amoxicillin in children receiving 90/6.4mg/kg/day of amoxicillin/clavulanate in divided doses q12h, derived from the mean plasma concentration profile of amoxicillin obtained in 5 children receiving 45/6.4mg/kg/day of amoxicillin/clavulanate in divided doses q12h



Mean plasma concentrations of amoxicillin shown for 90 mg/kg/day have been derived by doubling those obtained with a dose of 45 mg/kg/day, although please note that whereas the figure depicts the principle on mean data, calculations were based on individual data.

In the other pediatric study, 25000/446 [25], previously described, 19 subjects 3 months to 12 years of age, diagnosed with AOM, were administered *Augmentin* 90/6.4 mg/kg/day in divided doses q12h for 10 days. That study included the collection of a single blood specimen (for plasma) from each child for determination of amoxicillin concentration at one, two or three hours after dosing (approx. n= 6 at each time point). Unfortunately, the investigator felt it was impractical to keep the children in the clinic for more than 3 hours post dosing, and so the plasma concentration versus time profiles did not extend beyond 3 hours. Plasma concentrations of amoxicillin appeared to peak at 2 hours. From these data, it is possible to predict the rest of the profile by assuming an amoxicillin elimination half-life of 1.2 h (the mean value obtained in study 25000/382). This is illustrated with mean data in Figure 7. Using this approach, the mean $T > MIC$ for an amoxicillin MIC of 4 mcg/mL is approximately 38% (4.7 h/12 h), and this estimate has been published [26].

Figure 7 Mean plasma concentration vs time profile of amoxicillin in children receiving 90/6.4mg/kg/day of amoxicillin/clavulanate in divided doses q12h



* = actual data; later points are derived assuming a T1/2 of 1.2 h

In a recently completed study [49], the pharmacokinetics of *Augmentin* ES were determined in 18 pediatric patients (age range: 4 months to 11 years). Pharmacokinetic sampling was conducted on one occasion at frequent timepoints over the 12 hour interval. The data are summarized in Table 7.

Table 7 Pharmacokinetics (SD) of amoxicillin and clavulanic acid following administration of Augmentin ES to pediatric patients (n=18)

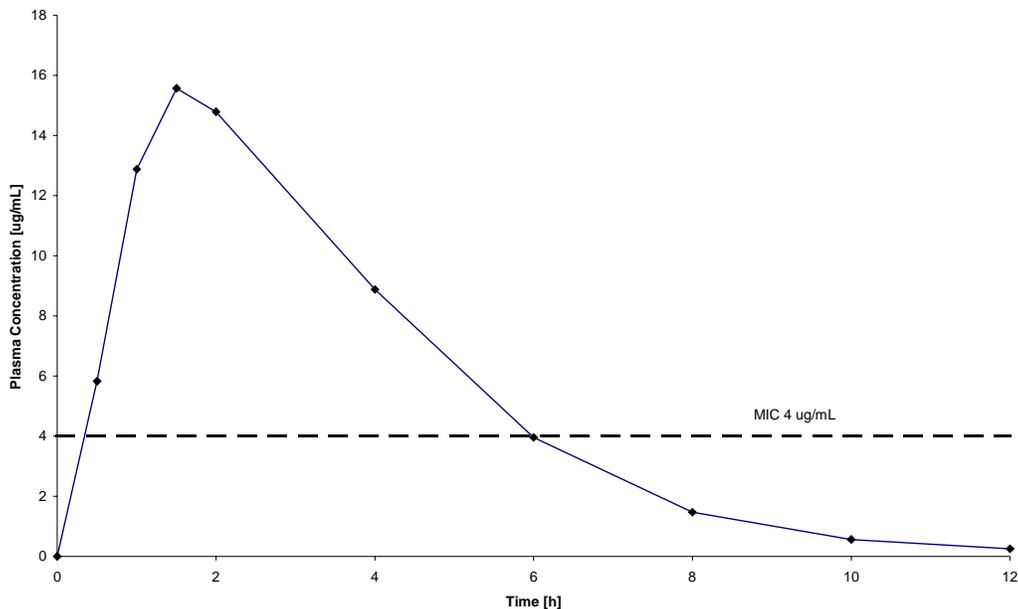
Parameter	Amoxicillin	Clavulanate
C _{max} [mcg/mL]	16.5 (7.1)	1.73 (0.871)
T _{max} [h]	2.00 (1.00 – 4.02)	1.07 (0.98 – 4.00)
AUC(0-t) [ug.h/mL]	62.6 (16.3)	4.13 (1.86)
T _{1/2} [h]	1.36 (0.35)	1.10 (0.29)*
CL/F [(L/h)/kg]	0.77 (0.26)	1.11 (1.09)*
T>MIC (h)	5.5 (1.25)	ND
T>MIC (%)	46 (10)	ND

*n=17

ND = Not determined

The mean amoxicillin plasma concentration versus time profile is depicted in Figure 8. In this study, a mean T>MIC of 46 % was achieved for an amoxicillin MIC of 4 mcg/mL. This is of the same order as that derived from previous studies (25000/382 [23] and 25000/448 [25]) which involved utilization of the known pharmacokinetic properties of amoxicillin. More importantly, it is within the range that has been correlated with bacteriological efficacy in AOM [8].

Figure 8 Mean amoxicillin plasma-concentration profile following administration of Augmentin 600 suspension (45/3.2 mg/kg) to paediatric patients (n=18)



3.2 Pharmacodynamics

The efficacy of amoxicillin and amoxicillin/clavulanate was compared in a neutropenic murine thigh model caused by strains of *S. pneumoniae* of differing susceptibility [28]. There was an excellent correlation between therapeutic efficacy and the duration that serum levels of amoxicillin exceeded the MIC and good efficacy was observed if levels exceeded the MIC for at least 30% of the dosing interval.

A neutropenic mouse pneumonia model was also used to assess the activity of amoxicillin against six strains of *S. pneumoniae* with MICs ranging from 0.01 to 4 mcg/mL [29]. In this study, when $T > MIC$ exceeded 40% the decrease in bacterial numbers was maximal and efficacy correlated directly with $T > MIC$ irrespective of the dosing interval. However, there was no significant decrease in numbers at $T > MIC$ of 25% or less of the dosing period.

Recently Craig and Andes [8] in a review of bacteriologic efficacy data from a number of otitis media clinical trials demonstrated that there is a significant correlation between the time for which beta-lactam antibiotic concentrations in serum were above the MIC and efficacy in otitis media. They showed that an 85

to 100% bacteriological cure rate was obtained when the T>MIC was 40% or higher [21].

3.3 Efficacy of amoxicillin/clavulanate against experimental respiratory tract infections caused by *S. pneumoniae*

A study was undertaken to examine the efficacy of the proposed 14:1 dose of amoxicillin/clavulanate (90 mg/kg/6.4 mg/kg/day, in two divided doses q12h) against strains of *S. pneumoniae* exhibiting decreased susceptibility to amoxicillin [27]. Amoxicillin/clavulanate was administered to simulate concentrations obtained in pediatric patients following administration of 45/3.2 mg/kg amoxicillin/clavulanate bid. Amoxicillin/clavulanate reduced the number of viable bacteria in the lungs of animals significantly ($p < 0.01$) compared with control animals against strains of *S. pneumoniae* with amoxicillin MICs up to and including 4 mcg/mL (Table 8). No effect ($p > 0.05$) was seen against *S. pneumoniae* strains with an amoxicillin MIC = 8 mcg/mL

Table 8 Activity of amoxicillin/clavulanate (14:1 dose) against penicillin-resistant *S. pneumoniae* in the rat RTI model

Strain	Amoxicillin MIC (mcg/mL)	\log_{10} CFU/lungs ⁺	
		Non-treated control (NTC)	Amoxicillin/clavulanate (90/6.4 mg/kg)
N137	2	6.97±0.30	2.62±0.85**
14319	4	6.80±0.62	4.28±0.82**
410101	4	7.11±0.45	3.91±0.81**
RS1	8	6.03±0.61	5.94±0.72

+ CFU – colony forming units

*Significantly different from NTC ($p < 0.01$)

**Significantly different from NTC and amoxicillin (22.5 mg/kg; $p < 0.01$)

3.4 Efficacy in Support of Breakpoint

In Study 536, the bacteriological response (bacteriological success or bacteriological failure) in patients with AOM due to *S. pneumoniae* was analyzed

at the on-therapy visit (day 4-6). The key clinical assessment was clinical response (clinical success or clinical failure) at the EOT visit (day 12-15).

The efficacy summary in support of breakpoint describes the bacteriological and clinical responses in patients with *S. pneumoniae* by amoxicillin/clavulanic acid MICs. The main efficacy presentations are for patients who completed the study by 05 November 1999. In order to reach the proposed goal of 14 evaluable patients with AOM due to *S. pneumoniae* isolates with an amoxicillin/clavulanic acid MIC ≥ 4.0 mcg/mL, investigators were directed to continue to enroll patients after 05 November 1999, the clinical cut-off for the PRSP analysis. Patients who completed the study after 05 November whose *S. pneumoniae* isolates at baseline had amoxicillin/clavulanic acid MIC = 4 mcg/mL or 8 mcg/mL, are also presented following the main efficacy presentations.

Bacteriological Response by Baseline Susceptibility (MICs) to Amoxicillin/Clavulanic Acid

Table 9 presents bacteriological response by baseline susceptibility (MICs) to amoxicillin/clavulanic acid. In the PP bacteriological *S. pneumoniae* population the overall bacteriological success rate was 97.6% (122/125; includes 3 patients who were bacteriological successes but missing amoxicillin/clavulanic acid MICs). Patients with *S. pneumoniae* at baseline with an amoxicillin/clavulanic acid MIC of 4 mcg/mL had a 100% (3/3) bacteriological success rate. Of the four patients with *S. pneumoniae* with an amoxicillin/clavulanic acid MIC of 8 mcg/mL, 75.0% (3/4) were associated with bacteriological success. Of the three bacteriological failures, one each occurred in patients whose *S. pneumoniae* isolate at baseline had amoxicillin/clavulanic acid MIC = 0.03 mcg/mL, MIC = 2 mcg/mL, and MIC = 8 mcg/mL.

Results were similar in the ITT bacteriological population of patients who had *S. pneumoniae* at baseline where overall 93.7% (149/159) of the patients were associated with bacteriological success.

Table 9 Bacteriological Response by Baseline *S. pneumoniae* Susceptibility to Amoxicillin/Clavulanic Acid (PP and ITT Bacteriology Population) - On-Therapy

<i>Augmentin ES</i>				
PP Bacteriological Population				
Bacteriological Response	Success		Failure	
	n/N	(%)	n/N	(%)
<i>S. pneumoniae</i> , Overall	122/125	(97.6)	3/125	(2.4)
<i>S. pneumoniae</i>				
Amoxicillin/clavulanic acid MIC, mcg/mL				
0.016	2/2	(100.0)	0	
0.03	61/62	(98.4)	1/62	(1.6)
0.06	9/9	(100.0)	0	
0.12	4/4	(100.0)	0	
0.25	10/10	(100.0)	0	
0.5	2/2	(100.0)	0	
1	3/3	(100.0)	0	
2	22/23	(95.7)	1/23	(4.3)
4	3/3	(100.0)	0	
8	3/4	(75.0)	1/4	(25.0)
ITT Bacteriological Population				
Bacteriological Response	Success		Failure	
	n/N	(%)	n/N	(%)
<i>S. pneumoniae</i> , Overall	149/159	(93.7)	10/159	(6.3)
<i>S. pneumoniae</i>				
Amoxicillin/clavulanic acid MIC, mcg/mL				
0.016	2/2	(100.0)	0	
0.03	76/79	(96.2)	3/79	(3.8)
0.06	11/14	(78.6)	3/14	(21.4)
0.12	5/5	(100.0)	0	
0.25	12/13	(92.3)	1/13	(7.7)
0.5	2/2	(100.0)	0	
1	3/3	(100.0)	0	
2	27/29	(93.1)	2/29	(6.9)
4	3/3	(100.0)	0	
8	5/6	(83.3)	1/6	(16.7)

Note: 3 patients are missing baseline amox/clav MICs, all of whom are in the bacteriological ITT and PP populations. They are counted as missing when displayed by amox/clav MIC and are thus not included in tabulations by MIC.

Amoxicillin/clavulanic acid, tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin content

In patients who completed the study after 05 November, 1999, one additional PP patient with *S. pneumoniae* at baseline with an amoxicillin/clavulanic acid MIC of 4 mcg/mL was associated with bacteriological success. When combined with patients completed before 5 November 1999, 100% (4/4) of patients with *S. pneumoniae* with an amoxicillin/clavulanic acid MIC of 4 mcg/mL were a bacteriological success. There were also two additional patients who completed after 05 November 1999 with *S. pneumoniae* with amoxicillin/clavulanic acid

MICs of 8 mcg/mL, of which one was a bacteriological success. In the combined analysis, 66.7% (4/6) of PP patients with *S. pneumoniae* MICs of 8 mcg/mL were associated with bacteriological success (Table 10).

In the ITT population, two additional patients who completed the study after 05 November 1999 had isolates of *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 mcg/mL, of which one was a bacteriological success. Likewise, at an amoxicillin/clavulanic acid MIC of 8 mcg/mL, there were two additional patients with *S. pneumoniae*, of which one was a bacteriological success. In the combined analysis, 80.0% (4/5) of patients with *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 mcg/mL were a bacteriological success (the one ITT failure was unable to determine due to being lost to follow-up) and 75.0% (6/8) of patients with *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 8 mcg/mL were a bacteriological success.

Table 10 Combined Analysis of On-Therapy Bacteriological Response in Patients with *S. pneumoniae* with Amoxicillin/Clavulanic Acid MICs = 4, 8 (PP and ITT Bacteriology Population)

		<i>Augmentin ES</i>			
		PP Bacteriological Population			
		Success		Failure	
Bacteriological Response		n/N	(%)	n/N	(%)
<i>S. pneumoniae</i>					
Amoxicillin/clavulanic acid MIC, mcg/mL					
	4	4/4	(100.0)	0	
	8	4/6	(66.7)	2/6	(33.3)
		ITT Bacteriological Population			
		Success		Failure	
Bacteriological Response		n/N	(%)	n/N	(%)
<i>S. pneumoniae</i>					
Amoxicillin/clavulanic acid MIC, mcg/mL					
	4	4/5	(80.0)	1/5	(20.0)
	8	6/8	(75.0)	2/6	(25.0)

Amoxicillin/clavulanic acid, tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin content

Clinical Response by Baseline *S. pneumoniae* Susceptibility to Amoxicillin/Clavulanic Acid

Table 11 presents clinical response at end of therapy by baseline *S. pneumoniae* susceptibility to amoxicillin/clavulanic acid. In patients with *S. pneumoniae*, the overall clinical success rate in the clinical PP population at the end of therapy was 89.3% (125/140; includes three patients who were clinical successes but missing amoxicillin/clavulanic acid MICs). In patients with isolates with amoxicillin/clavulanic acid MICs of 4.0 mcg/mL, the clinical success rate was 100% (3/3). The clinical success rate was 60.0% (3/5) in patients with *S. pneumoniae* isolates with amoxicillin/clavulanic acid MICs of 8.0mcg/mL. Seven of the 15 clinical failures were in patients with isolates with amoxicillin/clavulanic acid MICs = 0.030 mcg/mL, 2 each were in patients with isolates with amoxicillin/clavulanic acid MICs = 0.25 mcg/mL and MICs = 8.0 mcg/mL, and 4 were in patients with isolates with amoxicillin/clavulanic acid MICs = 2.0 mcg/mL.

Table 11 Clinical Response by Baseline *S. pneumoniae* Susceptibility to Amoxicillin/Clavulanic Acid (PP Clinical Population at End of Therapy)

Clinical Response	Augmentin ES PP Clinical Population			
	Success		Failure	
	n/N	(%)	n/N	(%)
<i>S. pneumoniae</i>				
Amoxicillin/clavulanic acid MIC, mcg/mL				
Overall	125/140	(89.3)	15/140	(10.7)
0.016	2/2	(100.0)	0	
0.03	66/73	(90.4)	7/73	(9.6)
0.06	11/11	(100.0)	0	
0.12	5/5	(100.0)	0	
0.25	8/10	(80.0)	2/10	(20.0)
0.5	2/2	(100.0)	0	
1	2/2	(100.0)	0	
2	20/24	(83.3)	4/24	(16.7)
4	3/3	(100.0)	0	
8	3/5	(60.0)	2/5	(40.0)

Note: In the clinical PP population 3 patients are missing amox/clav MICs. They are counted as missing when displayed by MIC and thus are not included in the overall numerator but are included in the overall denominator in the tabulations.

Amoxicillin/clavulanic acid, tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin content

In the clinical ITT population at the end of therapy in patients with isolates with amoxicillin/clavulanic acid MICs of 4 mcg/mL, the clinical success rate was 100% (3/3). The clinical success rate was 50.0% (3/6) in patients with *S. pneumoniae* isolates with amoxicillin/clavulanic acid MICs of 8 mcg/mL; there were 2 failures (33.3%) and 1 was missing a clinical response at the end of therapy visit. In patients with isolates with amoxicillin/clavulanic acid MICs < 4 mcg/mL, the clinical success rate was 83.0% (122/147), clinical failure rate was 10.2% (15/147) and 6.8% (10/147) were missing clinical assessment at the end of therapy.

In patients who completed the study after 05 November 1999, there was one additional (PP) patient with a *S. pneumoniae* isolate with an amoxicillin/clavulanic acid MIC of 4 mcg/mL, which made for a combined clinical success rate of 100% (4/4). At amoxicillin/clavulanic acid MIC of 8 mcg/mL, there were two additional *S. pneumoniae* patients who completed after 05 November 1999, both of which were a clinical success. The combined clinical success rate for patients with *S. pneumoniae* with an amoxicillin/clavulanic acid MIC of 8 mcg/mL was 71.4% (5/7; Table 12).

Table 12 Combined Analysis of Clinical Response in Patients with *S. Pneumoniae* with Amoxicillin/Clavulanic Acid MICs = 4, 8 (PP Clinical Population at End of Therapy)

Clinical Response	<i>Augmentin ES</i> PP Clinical Population			
	Success		Failure	
	n/N	(%)	n/N	(%)
<i>S. pneumoniae</i>				
Amoxicillin/clavulanic acid MIC, mcg/mL				
4	4/4	(100.0)	0	
8	5/7	(71.4)	2/7	(28.6)

Amoxicillin/clavulanic acid, tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin content

In the ITT population, there were two additional patients with *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 mcg/mL, of which one was a clinical success, the other was missing a clinical assessment at EOT. Likewise, at an amoxicillin/clavulanic acid MIC of 8 mcg/mL, there were two additional patients with *S. pneumoniae* which were a clinical success. In the combined analysis, 80.0% (4/5) of patients with *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 mcg/mL were a clinical success, and 62.5% (5/8) of patients with *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 8 mcg/mL were a clinical success at EOT.

3.5 Breakpoint Conclusion

Based on the pharmacokinetic parameters, pharmacodynamics of amoxicillin/clavulanic acid, *in vivo* animal and clinical data, the proposed breakpoints for amoxicillin/clavulanic acid for *S. pneumoniae* for the 14:1 *Augmentin ES* formulation are presented in Table 13. Susceptibility testing breakpoints for the *Augmentin ES* formulation for *Haemophilus* species and *Staphylococcus* species are unchanged from the current *Augmentin* formulations.

Table 13 Proposed amoxicillin/clavulanic acid breakpoints (mcg/mL) for Augmentin ES

Organism	Susceptible	Resistant
<i>S. pneumoniae</i>	$\leq 4/2$	$\geq 8/4$
<i>Haemophilus</i> species	$\leq 4/2$	$\geq 8/4$
<i>Staphylococcus</i> species	$\leq 4/2$	$\geq 8/4$

- *Augmentin* ES provides a mean T>MIC of 46% of the dosing interval for a MIC of 4 mcg/mL.
- Bacteriological and clinical response data presented here further support the proposed susceptibility breakpoint of $\leq 4/2$ mcg/mL for this formulation against *S. pneumoniae*.

4 Overall Conclusions

- Surveillance studies have demonstrated a dramatic reduction in antimicrobial susceptibility in *S. pneumoniae*, the primary pathogen associated with acute otitis media. In the US, the percentage of *S. pneumoniae* isolates from pediatric patients susceptible to penicillin in 1999 was 46.3%. Similarly, 60.4% of *S. pneumoniae* from pediatric patients were susceptible to ceftriaxone, and just over 54% were susceptible to the macrolides, azithromycin and clarithromycin. These data suggest that therapeutic options for treating infections caused by *S. pneumoniae* are becoming limited. The 14:1 amoxicillin/clavulanate suspension was formulated to provide a treatment option for infections in which resistant *S. pneumoniae* are suspected and beta-lactamase-producing organisms have not been ruled out.
- Pharmacokinetic/pharmacodynamic, *in vivo* and clinical data are presented which support a susceptible breakpoint of $\leq 4/2$ mcg/mL for the 14:1 suspension of amoxicillin/clavulanate.
- The pivotal *Augmentin* ES (amoxicillin/clavulanate potassium 90/mg/kg/day) clinical trials indicate that it is clinically and bacteriologically effective in the treatment of AOM, including cases involving penicillin resistant *Streptococcus pneumoniae* (PRSP). Further, the data support safe use of this formulation in pediatric patients. This product will provide the medical community with a new therapeutic tool in the empiric treatment of AOM, especially when the health care provider is concerned about the possible involvement of resistant respiratory bacteria.

5 References

1. CETRON M.S., JERNIGAN D.B., BRIEMAN R.F., AND THE DRSP WORKING GROUP. 1995. Action plan for drug-resistant *Streptococcus pneumoniae*. *Emerg. Inf. Dis.*, **1**, 64-65. [General/PUB-100BFL/1]
2. BLUMER J. 1998. Clinical perspectives on sinusitis and otitis media. *Pediatr Infect Dis J*, **17**, S68-72. [General/PUB-1007WS/1]
3. APPELBAUM P.C. 1992. Antimicrobial resistance in *Streptococcus pneumoniae*: An overview. *Clinical Infectious Diseases*, **15**, 177-183. [General/PUB-10050W/1]
4. DOERN, G.. 1995. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. . *Am J Med*, **99**, 3S-7S. [General/PUB-1005OX/1]
5. JACOBS, M.. BAJAKSOUZAN S ET AL 1999. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. *Antimicrob Agents Chemother*, **43**, 1901-1908. [General/PUB-1007WH/1]
6. Jacobs, M. The Alexander Project 1998: Penicillin and macrolide resistance in 2675 isolates of *Streptococcus pneumoniae* from 15 countries on five continents. Interscience Congress for Antimicrobial Agents and Chemotherapy. San Fransisco, CA, USA. [General/PUB-1009RD/1]
7. THORNSBERRY, C., M. JONES, M. HICKEY, Y. MAURIZ, J. KAHN AND D. SAHM. 1999. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in the United States, 1997 - 1998 . *J Antimicrob Chemother*, **44**, 749-759. [General/PUB-100B3S/1]
8. CRAIG WA AND ANDES D. 1996. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J*, **15**, 255-259. [General/PUB-1009VL/1]
9. BLOCK SL, HARRISON CJ, ET AL. 1995. Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media: risk factors, susceptibility patterns and antimicrobial management. *Pediatr Infect Dis J*, **14**, 751-759. [General/PUB-1007S3/1]

-
10. JACKSON MA ET AL. November 1996. Breakthrough Sepsis in Macrolide-Resistant Pneumococcal Infections. *Pediatr Infect Dis J*, **15:11**, 1049-1050. [General/PUB-1007WW/1]
 11. REID JR R, BRADLEY JS, HINDLER J. December 1995. Pneumococcal Meningitis During Therapy of Otitis Media with Clarithromycin. *Pediatr Infect Dis J*, **14:12**, 1104-1105. [General/PUB-1007WX/1]
 12. DAGAN R, LEBOVITZ E ET AL. 2000. Bacteriologic Efficacies of Oral Azithromycin and Oral Cefaclor in Treatment of Acute Otitis Media in Infants and Young Children. *AAC*, **44(1)**, 43-50. [General/PUB-1007WP/1]
 13. DAGAN R, ABRAMSON O, LEBOVITZ E ET AL. 1996. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *Pediatr Infect Dis J*, **15(11)**, 980-5. [BRL-025000/PUB-1009JD/1]
 14. DAGAN R, JOHNSON C, MCLINN S ET AL. 2000. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. *Pediatr Infect Dis J*, **19(2)**, 95-104. [General/PUB-100BFM/1].
 15. COHEN R. 1997. The Antibiotic Treatment of Acute Otitis Media and Sinusitis in Children. *Diagn Microbiol Infect Dis J*, **27**, 35-39. [General/PUB-1007WK/1]
 16. DOWELL S, BUTLER J, GIEBINK G, ET AL. 1999. Acute otitis media: management and surveillance in an era of pneumococcal resistance - a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J*, **18(1)**, 1-9. [General/PUB-1007HI/1]
 17. COHEN R, NAVEL M, GRUNBERG J, ET AL. 1999. One dose ceftriaxone vs. ten days of amoxicillin/clavulanate therapy for acute otitis media: clinical efficacy and change in nasopharyngeal flora. *Pediatr Infect Dis J*, **18(5)**, 403-409. [General/PUB-1007WV/1]
 18. HARRISON CJ. 1997. Using antibiotic concentrations in middle ear fluid to predict potential clinical efficacy. *Pediatr Infect Dis J*, **16:2**, S12-S16. [General/PUB-1007S5/1]
 19. Schrag, S.J., E. Zell, A. Schuchat, and C. Whitney. 2000. Evaluation of Sentinel Surveillance for pneumococci. Abstract 1797. Interscience Congress

-
- on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada.
[General/PUB-100BG0/1 .
20. BARRY B., MUFFAT-JOLY M., ET. AL. 1993. Effect of increased dosages of amoxicillin in treatment of experimental middle ear otitis due to penicillin-resistant *Streptococcus pneumoniae*. *Antimicrobial Agents and Chemotherapy*, **37 (8)**, 1599-1603. [General/PUB-100BG1/1]
 21. DRUSANO G.L. AND CRAIG W.A. 1997. Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *J. Chemother.*, **9 (Suppl. 3)**, 38-44. [General/PUB-1005NM/1]
 22. National Committee for Clinical Laboratory Standards. January 2000. Performance standards for antimicrobial susceptibility testing; Tenth Informational Supplement (Aerobic Dilution). M100-S10(M7). National Committee for Clinical Laboratory Standards, Wayne, Pa. [General/PUB-1009TV/1]
 23. SB Report HH-1017/BRL-025000/1. A parallel group study to estimate the steady state pharmacokinetics of amoxycillin and clavulanate in paediatric patients in the age range 1 month to 12 years administered Augmentin 45/6.4 mg/kg (twice daily) or 40/10 mg/kg/day (3xday) orally. Murdoch, RD., C Kaye, A Allen, AM Harris and E Allen. 28 April 1995.
 24. Todd PA and P. Benfield. 1990. Amoxicillin/Clavulanic Acid: an update of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs*, **39**, 264-307.[AGM8] [BRL-025000/PUB-1009BM/1]
 25. SB Report BRL-025000/RSD-1006FN/3. Comparison of amoxicillin concentrations in plasma and middle ear fluid following administration of Augmentin 45/3.2 mg/kg to pediatric patients with acute otitis media. Inglis, AM., SC Boike, D Jorkasky, GH McCracken, CM Kaye and N Zariffa. 14 April 1997.
 26. Burch, D. and G Moonsammy. 1999. Clinical profile of a new formulation of amoxicillin/clavulanate (A/C) for the treatment of acute otitis media (AOM). *Antimicrobial Agents and Chemotherapy*, **44 Supplement A 95**, 249. [AGM10290]. [General/PUB-100BFN/1]
 27. BRL-025000/1/RSD-100LRK/1. Efficacy of simulated human serum concentrations of amoxicillin/clavulanate against experimental respiratory

-
- tract infections caused by penicillin resistant strains of *S. pneumoniae*.
Woodnutt, G, Berry, V and Bryant, J. 20 June 1997.
28. ANDES, D. AND WA CRAIG. 1998. *In vivo* activities of amoxicillin and amoxicillin/clavulanate against *Streptococcus pneumoniae*: application to breakpoint determinations.. *Antimicrob Agents and Chemother*, **42(9)**, 2375-2379. [AMX6131] [General/PUB-1007Z9/1]
 29. PB-1046/BRL-025000/1. Efficacies of oral ampicillin, amoxicillin, amoxicillin/clavulanate and cefuroxime axetil against streptococcal respiratory infections in the mouse. Gisby, J and Woodnutt, G. 13 December 1994.
 30. CHARTRAND SA, PONG A. 1998. Acute otitis media in the 1990s: the impact of antibiotic resistance. *Pediatric Annals*, **27:2**, 86-95. [General/PUB-100BFP/1]
 31. DAGAN R, LEIBOVITZ E, GREENBERG D ET AL. 1998. Early eradication of pathogens from middle ear fluid during antibiotic treatment of acute otitis media is associated with improved clinical outcome. *Pediatr Infect Dis J*, **17**, 776-782. [General/PUB-1007WZ/1]
 32. JACOBS MR. 1996. Increasing importance of antibiotic-resistant *Streptococcus pneumoniae* in acute otitis media. *Ped Inf Dis J*, **15**, 940-943. [General/PUB-1007WJ/1]
 33. BLOCK SL, 1997. Causative Pathogens, antibiotic resistance and therapeutic considerations in acute otitis media. *Pediatr Infect Dis J*, **16**, 449-456. [General/PUB-1007WM/1]
 34. BARRY B, GEHANNO P, BLUMEN M AND BOUCOT I. 1994. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scand J Infect Dis*, **26**, 446-452. [General/PUB-1007RW/1]
 35. ZENNI MK, CHEATHAM SH, THOMPSON JM ET AL. 1995. *Streptococcus pneumoniae* colonization in the young child: association with otitis media and resistance to penicillin. *J Pediatr*, **127**, 533-537. [General/PUB-100BFR/1]
 36. DABERNAT H, GESLIN P, MEGRAUD F ET AL. 1998. Effects of cefixime or co-amoxiclav treatment on nasopharyngeal carriage of

-
- Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. *Journal of Antimicrobial Chemotherapy*, **41**, 253-258. [General/PUB-100BG4/1]
37. GHAFFAR F, MUNIZ LS, KATZ K ET AL. 2000. Effects of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. *Clinical Infectious Diseases*, **31**, 875-880. [General/PUB-100BFS/1]
38. CARLIN SA, MARCHANT CD, SHURIN PA ET AL. 1987. Early recurrences of otitis media: Reinfection or relapse. *J Pediatr*, **110**, 20-25. [General/PUB-1009XD1]
39. KALEIDA PH, BLUESTONE CD, ROCKETTE HE ET AL. 1987. Amoxicillin-clavulanate potassium compared with cefaclor for acute otitis media in infants and children. *The Pediatr Infect Dis J*, **6**, 265-271. [General/PUB-100BFT/1]
40. LEIBOVITZ E, GREENBERG D, PORAT N ET AL. Sept 2000. Clinical relapse of acute otitis media (CR-AOM) within one month after completion of treatment (Tx): Bacteriologic correlates. *Poster 1968 40th ICAAC* [General/PUB-100B2N/1]
41. STUTMAN HR AND ARGUEDAS AG. 1992. Comparison of cefprozil with other antibiotic regimens in the treatment of children with acute otitis media. *Clinical Infectious Diseases*, **14 (Suppl. 2)**, S204-208. [General/PUB-100BFV/1]
42. DAGAN R, ABRAMSON O, LEIBOVITZ E ET AL. 1997. Bacteriologic response to oral cephalosporins. Are established susceptibility breakpoints appropriate in the case of acute otitis media. *J Infect Dis*, **176**, 1253-1259. [General/PUB-100BFW/1]
43. MARCHANT CD, CARLIN SA, JOHNSON CE ET AL. 1992. Measuring the comparative efficacy of antibacterial agents for acute otitis media. The "Pollyanna Phenomenon". *J Pediatr*, **120**, 72-77 [General/PUB-1007WN/1] .
44. CARLIN SA, MARCHANT CD, SHURIN PA ET AL. 1991. Host factors and early therapeutic response in acute otitis media. *J Pediatr*, **118**, 178-83. [General/PUB-100BFX/1]

-
45. C. BLUESTONE. 2000. Clinical course, complications and sequelae of acute otitis media. *Pediatr Infect Dis J*, **19**, S37-46. [General/PUB-100BFZ/1]
 46. PICHICHERO, ET AL. 1997. Cefprozil treatment of persistent and recurrent acute otitis media. *Pediatric Inf Dis J*, **16**, 471-8. [General/PUB-100BG7/1]
 47. KLEIN, J.. 1993. Microbiologic efficacy of antibacterial drugs for acute otitis media. *Pediatric Infect. Dis. Journ.*, **12 (12)**, 973-975. [General/PUB-100BGB/1]
 48. KLEIN, J.. 1994. Otitis Media. *Journ. of Infect. Dis.*, **19**, 823-33. [General/PUB-100BGC/1]
 49. SB Document Number BRL-025000/RSD-101F99/1. A study to determine the pharmacokinetic profiles of amoxicillin and clavulanate over a 12 hour dosing interval in paediatric patients in the weight range of 5 to 40 kg receiving Augmentin at 45/3.2 mg/kg orally every 12 hours for up to 10 days. Interim p. I. Bromley, M. Stahl, N. Bird, A. Smith, T. White, A. Metcalf, A. Allen & C. Kaye. 30 November 2000.
 50. HOBERTMAN A, ET AL. 1996. Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. *Pediatr Infect Dis J*, **15**, 955-962. [General/PUB-1007WT/1]
 51. SB Report No. BRL-25000/RSD-1009XZ/3/CPMS-447. A comparison of the safety and efficacy of q12h Augmentin-90/6.4 mg/kg/day and q12h Augmentin 45/6.4 mg/kg/day in the treatment of acute otitis media in children. Rowinski, CA, Davies JT, Berkowitz E, Bevivin. Rowinski, CA, Davies JT, Berkowitz E, Bevivino M . 9 October 1997.
 52. HOWIE, V. AND PLOUSSARD, J.. 1969. The "In Vivo Sensitivity Test"- Bacteriology of Middle Ear Exudate. *Pediatrics*, **44**, 940-944. [General/PUB-100814/1]
 53. FELMINGHAM, D. GRUNEBERG, R.N. AND THE ALEXANDER PROJECT GROUP. 2000. The Alexander Project 1996-1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. . *Journal of Antimicrobial Therapy*, **45**, 191-203 [General/PUB-1007XN/1].