MEDICAL REVIEW OF NDA 50-755, AUGMENTIN 90 mg/kg/day ORAL SUSPENSION (14:1 formulation) FOR AOM DUE TO DRUG-RESISTANT *S. pneumoniae*

Applicant name: SmithKline Beecham Pharmaceuticals
Philadelphia, Pa 19101
Sharon Shapowal, R. Ph.

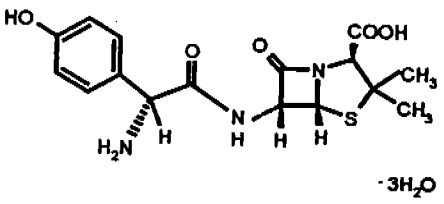
Date received: October 31, 1997
Date assigned : November 3, 1997
Date review begun: December 29, 1997
Date first draft completed: April 29, 1998
Date review completed: August 7, 1998

DRUG IDENTIFICATION

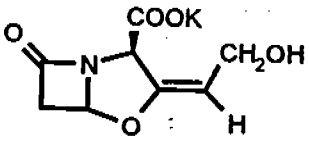
Generic Name: amoxicillin-clavulanate potassium
Proposed Trade Name: Augmentin DS
Formulation 14:1 formulation (amoxicillin-clavulanate 600mg/42.9mg per 5mL)

Pharmacologic Class: Combination antimicrobial agent consisting of a semisynthetic penicillin-class antibiotic, amoxicillin as a trihydrate, and a beta-lactamase inhibitor, clavulanic acid as the potassium salt

Chemical structure:
Amoxicillin

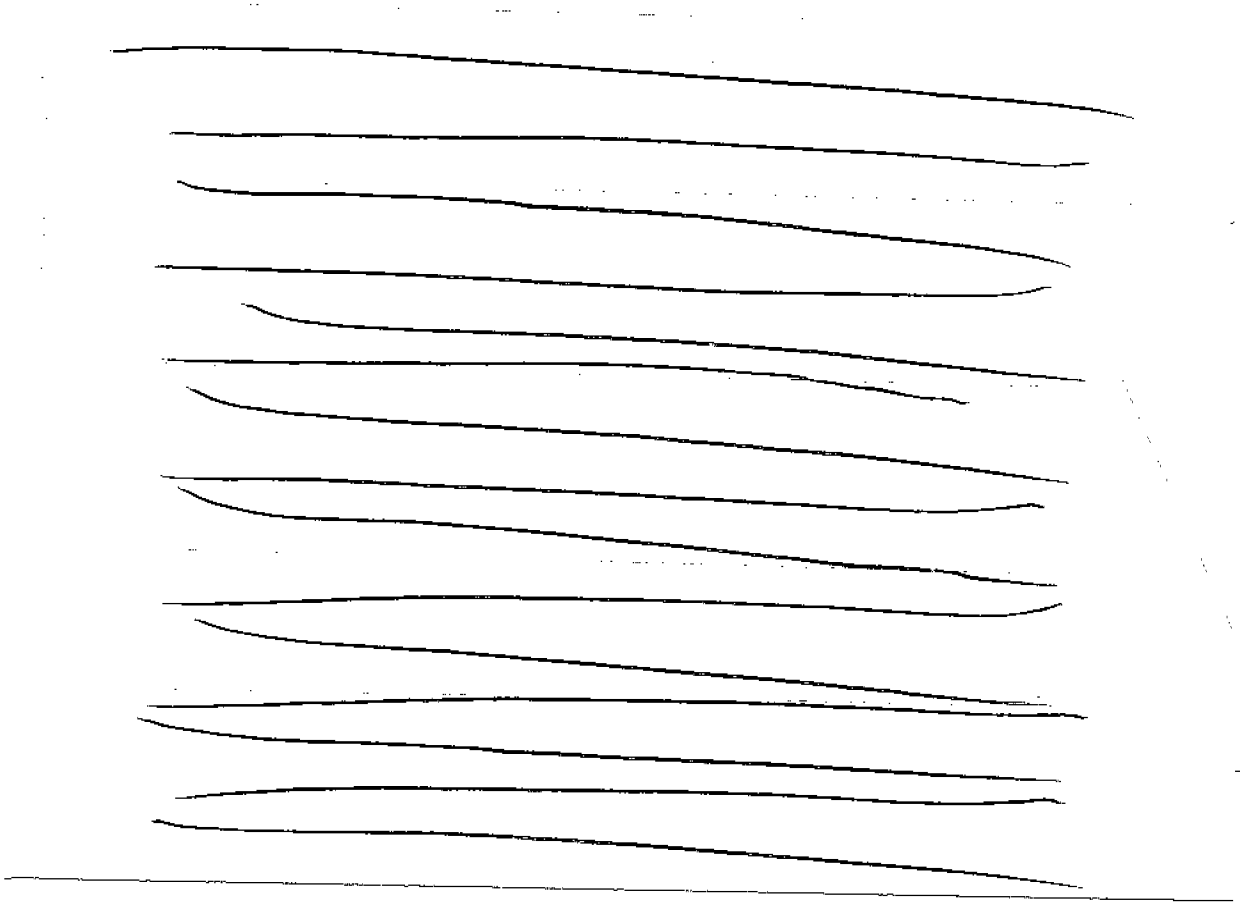


Clavulanic acid



Dosage Form: suspension
Route of Administration: oral

2 page(s) of revised draft labeling has been redacted from this portion of the review.



Related Drugs
Amoxicillin
Amoxicillin-clavulanic acid is available as 40mg/kg/day and 45mg/kg/day in the United States and is available in Europe as co-amoxyclav.

Material Reviewed
The new drug application was submitted in the form of an electronic submission. The Division of Anti-Infective Drug Products (DAIDP) Advisory Committee meeting minutes from July 1996 and March 1997 were reviewed. In addition, the clinical reviews of the following antimicrobial agents for the treatment of AOM were examined:

- Loracarbef
- Cefpodoxime
- Cefuroxime Axetil
- Ceftriaxone IM

Historical and Regulatory Background
August 8, 1995
Briefing package was requested by Carmen DeBellas, CSO for 8/24/95 teleconference between SB and FDA DAIDP; package containing information about the 14:1 amoxicillin-clavulanate potassium formulation was received from SB.

August 21, 1995
(From SB minutes of teleconference)
Teleconference with Division to discuss SB's drug-resistant *Streptococcus pneumoniae* (DRSP) program with the FDA:

1. the rationale for the development of the Augmentin 14:1 high dose formulation for the empiric treatment of *S. pneumoniae*
2. concerns raised by FDA attendees:
    - the use of two unapproved drugs in the same clinical trial (45mg/kg/day suspension, which was not approved at that time, and 90mg/kg/day suspension)
    - the regulatory dilemma of approval based on clinical safety data and T>MIC arguments, in the absence of correlation between clinical outcome and microbiology---sponsor argued that the low prevalence of resistant *S. pneumoniae* was not amenable to study

October 20, 1995
face-to-face meeting with senior level FDA staff (scheduled for October 30, 1995) canceled

January 5, 1996
A new protocol, 25000/446, entitled "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" was submitted.

May 31, 1996
Biopharmaceutics review of protocol 25000/446:

- dose of 45mg/kg b.i.d. very high, recommend close safety and tolerability monitoring
- information about the amoxicillin concentration profile in the middle ear after plasma concentrations decline is lacking and unpredictable
- information on the precision of sampling collection times not provided

October 3, 1996
Protocol 25000/447 entitled "A comparison of efficacy and safety of q 12 hours Augmentin 90/6.4 mg/kg/day and q 12 hours Augmentin 45/6.4 mg/kg/day in the treatment of acute otitis media in children: A randomized double blind, multicenter, comparative study" was submitted.

October 21, 1996
Medical officer's review of protocol 25000/447:

- concerns raised regarding the study coordinator performing both blinding and randomization
- "There is no microbiologic component to the efficacy analysis at the present time and no inference can be made about the potential for the effectiveness of the high-dose regimen on unapproved causative agents."
- "inability to draw any conclusion about the effectiveness of the antibiotic agent in the therapy of PRSP without microbiologic data"
- appeared that only a dosage change could be obtained given the lack of bacteriologic information

Concerns conveyed by reviewer, Dr. Alivisatos to Sharon Shapowal, SB US Regulatory Affairs

October 24, 1996
SB request for formal face-to-face meeting with the Division and senior FDA staff to secure agreement on the Augmentin 14:1 project

December 5, 1996
use of ClinPhone (to maintain blinding) submitted in amendment to protocol 25000/447

December 19, 1996
Internal DAIDP meeting to discuss the use of PK/PD study, pharmacokinetic/pharmacodynamic surrogates, and clinical safety study (without a bacteriologic study) for approval
Recommendation: sponsor could submit information in NDA

January 23, 1997
(from SB meeting minutes)
Face-to-face meeting between FDA and SB to discuss whether a clinical safety study, and clinical PK data including middle ear fluid levels of amoxicillin, animal modeling, and T>MIC arguments, in the absence of microbiologic data, would be sufficient to support submission of NDA for the Augmentin 14:1 formulation; agreed that SB proposal reviewable

December 16, 1997
Face-to-face meeting with representatives from SB to discuss concerns regarding the application; the medical reviewer questioned:

- the use of a PK/PD surrogate (T>MIC) for clinical efficacy especially for the approval of Augmentin DS for the empiric treatment of drug-resistant *S. pneumoniae*
- the lack of a microbiology study to support the clinical efficacy study, especially since an indication for a resistant organism was being sought

December 30, 1997
NDA filed

January 21, 1998
Discussion between this medical reviewer and SB representative regarding about the review time for the NDA; SB representative recognized that Subpart H regulation has no time specification

April 10, 1998 Teleconference
Reviewer inquired about demographic and safety information tables which excluded center 002 patients

May 6, 1998
Telecon with Ms. Shapowal to raise two review questions regarding study 25000/446, Pivotal pharmacokinetic study submitted in the NDA

- clarification sought regarding discrepancy in the number of patients randomized to this study---19 patients reported in SB submission vs. 30 patients in the published literature report of this study (Seikel K, Shelton S, and McCracken G. Ped Inf Dis J. 1997)
- reviewer unable to find case report forms (CRFs) for this study

May 18, 1998
Facsimile received from SB regarding issues raised in May 6, 1998 teleconference:

- clinical investigator confirmed typographical error in the published results— there were 19, not 30, patients enrolled in the trial
- case report forms for study 446 were not submitted with the application but are available; reviewer requested CRF for study 446 be forwarded (paper form acceptable)

May 29, 1998
Responses to the issues raised at face-to-face meeting on December 16, 1997, received from SB; packet included draft synopsis of an open-label clinical-microbiologic study of Augmentin 90mg/kg/day in children with AOM due to *S. pneumoniae*

June 3, 1998
Case report forms for study 25000/446 received

REGULATORY GUIDANCE DOCUMENTS

The Points to Consider Document of the Division of Anti-infective Drug Products
For acute otitis media, the document suggests 2 clinical trials:

- one clinical only study—statistically adequate and well-controlled, multicenter comparative—to establish equivalence to an approved product using rigid case definitions; baseline tympanocentesis is not necessary but is strongly encouraged for therapeutic failures
- one open, microbiological clinical study with tympanocentesis at study entry and post-therapy tympanocentesis of failures

The IDSA/FDA guidelines

- The control drug should be one with proven activity against *Hemophilus influenzae, Moraxella catarrhalis* and *S. pneumoniae*.
- All children who receive systemic antibacterial agents within the 7 days before study entry should be excluded.
- Aspirates from those who fail therapy clinically at least 72 hours after drug initiation are required.
- The test-of-cure (TOC) visit should be done 1-2 weeks after the completion of therapy, and organism-specific efficacy response rates should be evaluated.

Divisional Evaluability Criteria–Evaluating Clinical Studies of Antimicrobials
The following criteria are recommended for the evaluability of patients.
For clinical evaluability, the clinical diagnosis of OM must be based on:

1. history
2. physical examination
3. pneumatic otoscopy findings:
   - swollen bulging tympanic membrane (TM) which may be erythematous (a hyperemic tympanic membrane or fullness is not sufficient)
   - loss of light reflex
   - abnormal TM mobility owing to fluid behind the membrane and edema of the membrane, and
4. tympanometry

For microbiologically evaluability, the diagnosis of AOM must be based on the results of tympanocentesis. Patients must have:

- a sample from the involved/affected ear(s)
- isolation of bacterial organisms
- *in vitro* susceptibility testing of the isolate to the study and control drugs

To be evaluable, a patient should receive within 80-120% of the prescribed dose and dosing regimen. A patient who receives at least 72 hours of therapy and is not doing well may be called a failure. Tympanocentesis is recommended for patients judged to be failing therapy.

<u>Advisory Committee Recommendations (March 1997)</u> regarding AOM Evaluability Criteria

- larger microbiologic studies needed to show bacteriologic cure and assure that the drug has significant antimicrobial effect on the illness for which it is approved
- number of patients evaluated in clinical microbiologic studies should be increased, with emphasis on those with penicillin-intermediate or penicillin-resistant organisms
- patients who fail therapy should have tympanocentesis

NON-CLINICAL STUDIES

CHEMISTRY/MANUFACTURING CONTROLS
See review by Chemist, Andrew Yu, Ph.D.
The CDER Labeling and Nomenclature Committee found the names Augmentin 14:1 and Augmentin DS unacceptable.

ANIMAL PHARMACOLOGY/TOXICOLOGY
No data were submitted for review.

MICROBIOLOGY
See review by Microbiologist, James R. King, Ph.D.

Medical Reviewer's comments:
The applicant has noted in the microbiology section of the submission that the spectrum of the antibacterial activity of clavulanate, other than beta-lactamase inhibition, is not clearly defined yet.

HUMAN CLINICAL EXPERIENCE
Foreign Experience
Clinical trials were conducted in 5 countries using higher doses of Augmentin---60/15mg/kg/day and 70/10 mg/kg/day, and in these studies no safety problems were encountered.
Approval for Amoxicilin clavulanic acid 80mg/kg/day for infants 1-30 months of age was granted in France in 1992.

BACKGROUND
Acute otitis media (AOM) is one of the most common infectious disease in children; it is the leading childhood diagnosis for which antimicrobial agents are prescribed in the outpatient setting in the US today (Nyquist et al., JAMA 1998).

Epidemiology
The peak age specific attack rate is highest in children between 6-24 months of age, and by 1 year of age, approximately 62% of children have had at least one episode of acute otitis media. Children at greatest risk for AOM include males, Native Americans and Eskimos, infants with early onset of disease, group day-care attendees, bottle-fed infants, and those exposed to passive smoke and environmental antigens (Bluestone CD and Klein JO. Otitis Media in Infants and Children, 1995).

Pathophysiology and Microbiology
Acute otitis media is often preceded by a viral infection, resulting in congestion of the upper respiratory tract. Obstruction of the Eustachian tube leads to accumulation of fluid in the middle ear and AOM results when the fluid becomes colonized with multiplying nasopharyngeal bacteria.
The organisms most commonly associated with AOM are *S. pneumoniae,* non-typeable *Hemophilus influenzae,* and *Moraxella catarrhalis. S. pneumoniae* is the most important bacterial cause of AOM, accounting for about 40-50% of cases, while *H. influenzae* and *M. catarrhalis* have been associated with 25% and 10% of cases, respectively. Nearly 40% and 75% of *H. influenzae* and *M. catarrhalis* strains, respectively, produce beta-lactamase. Up to 15% of middle ear fluid cultures reveal two organisms, and the pathogens found in the right and left ears may differ in up to 20% of patients. In 20 to 30% of specimens, no pathogens or non pathogens, many of which are respiratory viruses, are found.

Clinical Presentation and Diagnosis

The diagnosis of AOM is not standardized or validated and specific criteria are not established. Practitioners have vastly differing criteria for the diagnosis of AOM and even in clinical trials, different criteria have been used ((Dowell S et al., Pediatrics 1998; 101 Suppl: 165-71). Children with acute otitis media have rapid onset of signs and symptoms which may including fever, irritability, headache, anorexia, vomiting and diarrhea. The clinical diagnosis of AOM is dependent on a thorough pneumatic otoscopic examination of the ear. Patients with AOM will have a red or pale yellow, distinctly bulging and opacified tympanic membrane with cloudy or yellow fluid visible behind it, and may have perforation with associated (new) otorrhea, and local signs of acute infection such otalgia, and fever (Bluestone CD and Klein JO. Otitis Media in Infants and Children. 1995; Kaleida P. Contemporary Pediatrics, Sept 1997). Although it is the most specific symptom referable to AOM, otalgia can also be associated with otitis externa, serous otitis media, chronic otitis media, and as referred pain from non-otogenic sources (Bluestone CD and Klein JO. Otitis Media in Infants and Children, 1995; Maxson S and Yamauchi T. Ped in Review 1996).

Up to 42% of cases of AOM are associated with preceding viral URI and signs and symptoms such as fever, rhinorrhea, irritability, cough, vomiting, and diarrhea; however, the presence of URI symptoms alone is not enough to differentiate AOM from OME (Maxson S and Yamauchi T. Ped in Review 1996; Dowell S et al., Pediatrics 1998; 101 Suppl: 165-71).

Tympanometry, and acoustic reflectometry may be performed to support the clinical diagnosis of AOM. Tympanocentesis and culture of the middle ear fluid are necessary for the microbiologic diagnosis of AOM. Because the results of cultures from both ears are disparate (in 20% of cases), each diseased ear must be aspirated and the outcome assessed separately.

Natural History

Up to 80% of cases of AOM due to a bacterial pathogen will resolve spontaneously, that is, improve without treatment with antibacterial drugs. Clinical improvement and resolution may occur due to spontaneous discharge of the contents of the middle ear through the Eustachian tube, or by spontaneous perforation of the tympanic membrane. Spontaneous resolution is more likely to occur in children older than 2 years with AOM complicated by TM perforation, and in patients with no underling anatomic deformity.

Spontaneous resolution rates are highest for *Moraxella catarrhalis* and least for *S. pneumoniae.* Antibacterial agents have a 14% advantage over no treatment or placebo, meaning that 7 patients must be treated to ensure that the 1 patient with AOM which will not resolve spontaneously gets cured (Rosenfeld RM. Ped Inf Dis J 1995;14:731-8).

Therapeutic options

The optimal treatment for children with penicillin-resistant pneumococcal AOM is not known. Because a failure rate of 10% is expected when amoxicillin is used to treat beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis,* and, only 5% of pneumococci are highly resistant to penicillin, amoxicillin is still the antimicrobial agent of first choice for the treatment of uncomplicated AOM (Barnett ED and Klein JO. Ped Clinics of NA, 1995). The ratio of antibiotic concentration in the middle ear fluid (MEF) to minimum inhibitory concentration (MIC) of the organisms should be a consideration in assessing the clinical efficacy of a new agent.

With treatment, acute signs and symptoms of infection are expected to improve significantly within 48-72 hours. Follow-up assessments, which can be extended as far out as 4-6 weeks after the initiation of treatment, should be made to determine the recovery from the acute infection and the persistence of middle ear effusion.

Despite treatment with the appropriate antimicrobial agents, the middle ear effusion in AOM may persist for weeks to months after treatment--50% of children will have fluid in the middle ear at 1 month and 10% at 3 months, respectively.

The following antimicrobial agents are approved for the treatment of (acute) otitis media:
amoxicillin
amoxicillin-clavulanate
trimethoprim-sulfamethoxazole
erythromycin-sulfisoxazole
cefixime
cefpodoxime
cefprozil
cefaclor
loracarberf
cefuroxime axetil
ceftriaxone IM
ceftibuten
clarithromycin
azithromycin

Resistance
The overall prevalence of penicillin-nonsusceptible pneumococci in pediatric patients with AOM depends on the population studied but is highest in day-care attendees who have received recent treatment with antimicrobial agents, especially beta-lactams. Other risk factors for colonization or infection with penicillin-nonsusceptible pneumococci include recurrent AOM, age less than 36 months, and the winter season. Treatment failures have been associated with resistant pneumococcal infections and the risk of treatment failure will likely increase as the levels of resistance increase.

Adjunctive therapies
Decongestants, antihistamines and corticosteroids have had no obvious benefit on the treatment of acute otitis media. However, the combination of corticosteroids and antimicrobials may have some favorable benefit in preventing middle ear effusions (Conrad, D Ped Annals, 1998). In general, adjunctive therapies are not necessary to achieve clinical resolution and have no favorable impact on the long-term outcome.

INTRODUCTION TO CLINICAL TRIALS

General Overview
The applicant has submitted the results of 2 pivotal studies to support the proposed higher dose to treat acute otitis media due to drug-resistant *S. pneumoniae* . An open-label, single center pharmacokinetic/ pharmacodynamic study was conducted. Blood specimens were collected 1,2,3 hours after dosing with Augmentin 45/3.2 mg/kg for the determination of amoxicillin concentrations; middle ear fluid concentrations in 19 children, 3 months to 12 years of age with acute otitis media were measured in specimens obtained by tympanocentesis.
A single phase 3 well-controlled pivotal clinical study, in which the clinical efficacy and safety of *Augmentin* 90/6.4 mg/kg/day q12h for 10 days vs. *Augmentin* 45/6.4 mg/kg/day q12h for 10 days to treat AOM in 453 children, 3 months to 12 years of age, was conducted. Evaluations were done 12-14 and 22-28 days after the initiation of therapy.
No bacteriologic study was conducted.

N=19

N=453

RATIONALE (text taken from electronic submission of NDA 50-755)
SmithKline Beecham recognizes that *Streptococcus pneumoniae* is a non-beta-lactamase-producing organism susceptible in most cases to amoxicillin alone. Thus, one can question the need for the second component of *Augmentin* (the beta-lactamase inhibitor, clavulanate

potassium) in treating *S. pneumoniae* infections, and the need for developing *Augmentin* for the above-stated indication. The rationale is two-fold:

1. First, medical treatment of otitis media typically involves antibiotics selected empirically. Physicians do not routinely perform tympanocentesis or base antibiotic selection on culture results. Currently, the 4:1 and 7:1 ratio formulations of *Augmentin* are indicated for use in treating otitis media. Given empiric antibiotic selection, and the three most likely pathogens in otitis media *(S. pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*), development of a higher strength *Augmentin* (14:1 ratio) to "cover" the more resistant *S. pneumoniae,* as well as provide coverage against the two most likely other pathogens (b-lactamase producers), in acute otitis media was deemed appropriate.

2. Second, there is a mounting body of evidence, from independent investigations, demonstrating that clavulanate contributes to the activity of amoxicillin against *S. pneumoniae.* The mechanism is, as yet, unknown and unrelated to beta-lactamase inhibition.

SmithKline Beecham recognizes that empiric use as a regulated indication is non-traditional, despite physician practice. It is also recognized as non-traditional to develop an antibiotic prior to national, high level occurrence of the resistant target pathogen. Traditional antibiotic development includes bacteriologic data correlated to clinical efficacy in the pivotal clinical trial. However, high level resistance in *S. pneumoniae* (i.e. MIC of 2 to 4 mcg/mL to amoxicillin; 4 to 8 mcg/mL to penicillin) is not yet prevalent enough to make clinical studies with bacteriologic confirmation practical. However, efficacy can be predicted from pharmacodynamic arguments. The sponsor has chosen to develop the *Augmentin* 14:1 product prior to greatest market need, rather than to wait for high level resistance and then begin product development. The sponsor wishes to respond to requests from the infectious disease community for the availability of high-dose amoxicillin regimens.

Intended Use (as stated in NDA submission)
Augmentin-90 is intended to be used for the empiric treatment of acute otitis media in children where infection with either *S. pneumoniae* of reduced susceptibility to penicillin (i.e., MIC≤4 mcg/mL) or beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* is suspected.

Medical Reviewer's comments:
The single clinical only study is not adequate to support the claim of efficacy for acute otitis media due to resistant S. pneumoniae.
There is no Divisional precedent for the approval of agents based on T>MIC. Under current Divisional Guidelines, T>MIC and other PK/PD parameters are recognized as adjuncts to clinical trials, which are still necessary to demonstrate efficacy. More data are needed from clinical trials to adequately establish these surrogates as reliable predictors of clinical and/or bacteriologic outcome.

Patients with AOM due to bacteria cannot be easily distinguished from those with viral OM, OME or OM due to other pathogens in a clinical study. It is also not possible to know the proportion of cases that have resolved spontaneously because the microbiologic etiology is not defined, and the proportion of patients with each pathogen is unknown. Additionally, a clinical only study does not help explain all treatment failures because in some cases of AOM relapses and failures, no bacterial pathogens are found (Canafax D et al. Pediatr Infect Dis J 1998). For example if present, bacteriologic failures with *H. influenzae,* although so far reported only by Patel J et al., (J Pediatr 1995) cannot be documented in a clinical-only study.

Clinical studies are not as effective as microbiologic studies at detecting significant differences between the activity of 2 agents, without large sample sizes, because of the high spontaneous

resolution rates. Therefore, clinical outcomes alone are not good predictors of success and bacteria-specific response rates are needed to assess the adequacy of a new drug regimen.

Empiric treatment is not appropriate in the face of increasing pneumococcal resistance to antimicrobial agents.

Empiric therapy is not appropriate in areas with penicillin-resistant pneumococci; a bacteriologic diagnosis should be sought and the appropriate treatment rendered on the basis of these findings (Dowell et al, 1998). Because therapy for AOM is almost always empirical, microbiologic efficacy against the main pathogens associated with AOM, particularly drug resistant *S. pneumoniae,* should be documented.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

See review by Biopharmaceutist, He Sun, Ph.D.

Pivotal PK Study 25000/446

Study 25000/446 was an open-label, single center study of patients presenting with AOM as assessed at screening. Middle ear fluid (MEF) and plasma concentrations of amoxicillin were determined after administration of a single oral dose of *Augmentin* 45/3.2 mg/kg, and the tolerability of the *Augmentin* 90/6.4 mg/kg/day q12h for 10 days was evaluated. The A blood specimen (1 mL by fingerprick or venipuncture) and an MEF specimen (by tympanocentesis) were collected at 1, 2,or 3 hours after dosing based on a randomization schedule (six patients at each timepoint). After 3 hours, patients were discharged home to complete a 10-day course of the study medication. The parent/legal guardian of the child was telephoned between Days 3 and 5 of the therapy and days 12 and 14 to ask about adverse events (AE), to determine if the patient had improved, and if the medication was tolerated (See Outline of Study Procedures). Descriptive statistics were calculated for demographic data, as well as for plasma and MEF concentrations of amoxicillin. No formal statistical analysis was performed.
Nineteen patients were enrolled in the study.

Primary Objective	to determine the middle ear fluid (MEF) and plasma concentrations of amoxicillin at 1, 2, and 3 hours after administration of a single oral dose of *Augmentin* 45/3.2 mg/kg
Secondary Objective	to evaluate the tolerability of the *Augmentin* 45/3.2 mg/kg q12h (90/6.4 mg/kg/day) for 10 days.
Study dates	29 Feb 1996-3 June 1996
Location	US; 1 site
Study drug	*Augmentin* 90/6.4 mg/kg/day every 12 hours
Randomized	19 (12 males and 7 females); 11 black, 6 Hispanic, 2 white
PK Evaluable	14/19
	2 subjects: w/out MEF (and blood) specimens
	3 subjects: MEF samples grossly bloody (MEF amoxicillin concentrations not calculated)
Adverse events	diarrhea in 5/19 patients; one withdrawal as a result of diarrhea

Outline of Study Procedures-Study 446

	Diagnosis/Screening Visit	Day 1			Interim Evaluation (telephone) Days 3-5	End of Therapy Evaluation (telephone) Days 12-14
	Pre-dose	0 Hour	1, 2 or 3 Hours†	12 Hours		
Informed Consent	✓					
Medical History	✓					
Physical Exam	✓				✓	
Medication Dosing		✓		✓*		
Blood Specimen for PK			✓			
MEF Specimen for PK			✓			
Discharge			✓			
Assessment of Response					✓	
Compliance					✓	✓
Concomitant Medications					✓	✓
Adverse Experiences		✓§	✓		✓	✓

* Augmentin® continued at a dose of 45/3.2 mg/kg every 12 hours for a total of 10 days

§ Baseline assessment of Signs and Symptoms

† Based on a randomization schedule provided by SmithKline Beecham

Table 1 Demographic Data - study 25000/446

Group	Parameter	Age (months)	Weight (kg)	Height (cm)	Race
Male	n	12	12	12	Black = 6
	Mean	31	15.1	93	Hispanic = 4
	SD	23.6	5.88	18.1	White = 2
	Range	(7 - 96)	(8.8 - 29.0)	(67 - 132)	
Female	n	7	7	6*	Black = 5
	Mean	35	15.0	101	Hispanic = 2
	SD	24.6	4.38	14.5	
	Range	(9 - 84)	(9.9 - 24.0)	(87 - 127)	
Total	n	19	19	18*	Black = 11
	Mean	32	15.0	96	Hispanic = 6
	SD	23.3	5.24	16.9	White = 2
	Range	(7 - 96)	(8.8 - 29.0)	(67 - 132)	

* Height not determined for Subject 005

Sixteen patients completed the study. Three patients were withdrawn–1 for an adverse event and 2 for non-compliance. Pharmacokinetic evaluation was performed on samples from 14/19 enrolled subjects. MEF was not recovered from 2 subjects, and blood samples were not drawn for these subjects. MEF amoxicillin concentrations could not be calculated for an additional 3 subjects because the MEF samples were grossly bloody.

The table below presents the amoxicillin concentrations in MEF and plasma.

Table 2 Concentrations of Amoxicillin in Plasma and Middle Ear Fluid - study 25000/446

Timepoint		Amoxicillin Concentration in Plasma (mcg/mL)	Amoxicillin Concentration in MEF (mcg/mL)	Amoxicillin MEF/Plasma Ratio
1 hour	n	5	4	4
	Mean	7.7	3.2	0.32
	Median	9.3	3.5	0.30
	Range			
2 hour	n	7	5	5
	Mean	15.7	3.3	0.21
	Median	13.0	2.4	0.20
	Range			
3 hour	n	5	5	5
	Mean	13.0	5.8	0.53
	Median	12.0	6.5	0.62
	Range			

The plasma amoxicillin concentration peaked at 2 hours, while the MEF concentration was still increasing at 3 hours, and may have been continuing to increase for some time thereafter.

Medical reviewer's comments:

The calculation of T>MIC in MEF is not possible since the MEF concentration was still increasing at three hours. Patients who were failing therapy were to be seen within 24 hours of the telephone contact.

Adverse Experiences
A total of fifteen (15) adverse experiences (AEs) were reported for ten (10) subjects. There were no serious AEs or deaths. Five (5) AEs were considered to be unrelated to study medication (four subjects with earache and one with fever). The most common AE reported was diarrhea in 5 patients, and one subject withdrew from the study as a consequence of diarrhea, which began after one dose of study medication. One subject had abdominal pain and another experienced vomiting.

Medical reviewer's comments:
Although the number of patients is small, the incidence of diarrhea is quite high.

Study 25000/382 - Supportive pediatric data
In study 25000/382 (Augmentin NDA 50-725), the steady-state pharmacokinetic profiles of amoxicillin and clavulanate in 5 children 1 month-12 years were evaluated after Augmentin 45/6.4 mg/kg/day q12h. On the day of the pharmacokinetic assessment (>48 hours to <9 days after start of therapy), blood samples were drawn pre-dose, hourly for up to eight hours, and 12 hours after the designated dose.
To estimate T>MIC and percent values for 90 mg/kg/day, the individual plasma concentration-time data for subjects administered 45 mg/kg/day were doubled, and the corresponding values calculated, as presented in the table below.

Table 3 Plasma T>MIC values for 45/6.4 and 90/6.4 mg/kg/day Augmentin doses - study 25000/382

	Amoxicillin T>MIC in hours (%)			
	0.5 mcg/mL	1.0 mcg/mL	2.0 mcg/mL	4.0 mcg/mL
45 mg/kg/day (Actual)	7.27 (61)	6.05 (50)	4.92 (41)	3.37 (28)
Range				
90 mg/kg/day (Calculated)	8.01 (67)	7.28 (61)	6.03 (50)	4.95 (41)
Range				

Conclusions and Recommendations of Biopharmaceutics Reviewer, Dr. He Sun 7/13/98
- An extrapolated drug concentration and T>MIC value based on a dose that is half the proposed dose is not acceptable.
- T>MIC values, in plasma and MEF, cannot be determined from the data reported from study 446.
- The sponsor did not provide acceptable support for the Augmentin 90mg/kg/day resulting in a T>MIC in MEF of 40% or more of the dose interval for the indicated pathogen.

Medical reviewer's comments:
1. T>MIC for Augmentin 90mg/kg/day
The results in the table above are based on an estimated (extrapolated) of T>MIC from Augmentin 45mg/kg/day data in only 5 patients. These calculations of T>MIC are for plasma only; no data have been provided for the MEF. No data are available in the application on T>MIC in the plasma or in the MEF for Augmentin 90mg/kg/day.

When T_{MIC} is in the 40-50% range for the dosing interval or for 24 hours, favourable clinical outcomes in the 80-85% range can be expected. Amoxicillin alone at the currently approved doses appears to provide adequate drug concentration for the treatment of penicillin resistant strains, based on a T>MIC argument and on the current amoxicillin breakpoints for pneumococcus as set by NCCLS:

susceptible	≤0.5 ug/mL
intermediate	1 ug/mL
resistant	≥2 ug/mL. This is summarized in the table below:

Table T>MIC for Amoxicillin formulations

Formulation	Plasma T>MIC (% of interval) for Amoxicillin 1.0 mcg/mL	2.0 mcg/mL
Amoxicillin 40mg/kg/day		
Amoxicillin 45mg/kg/day		
Amoxicillin 75mg/kg/day		
Amoxicillin 90mg/kg/day		

Craig and Andes, Ped Infect Dis J, 1996; Reed M. Ped Infect Dis J, 1996; Canafax D et al., Pediatr Infect Dis J 1998; and SB NDA 50-755.

From the results in the table above:

- the same killing effect can be predicted to be achieved with amoxicillin alone, and
- lower concentrations of amoxicillin may achieve the desired T>MIC.

Following a single dose of amoxicillin 25mg/kg, total MEF concentrations of children with AOM were measured to predict the T>MIC for amoxicillin (Canafax et al., 1998). MEF amoxicillin concentrations were maintained above the MIC for intermediately resistant pneumococci for 50% of the dosing interval, and for 31% of the dosing interval for resistant pneumococci.

2. Clinical Data to support T_{MIC} as surrogate endpoint for efficacy are limited.

PK/PD surrogates have been studied mainly *in vitro* in and animal models; human studies to support a relationship between T_{MIC} and microbiologic efficacy of beta lactams are few. There appears to be good correlation between the animal models and the few studies in humans for beta-lactams; however, since the validity of these parameters has been demonstrated to a limited extent, more clinical data is needed (Turnidge JD Clin Infect Dis 1998; Cars O. Diagnostic Microbiol Infect Dis 1996).

3. Do peak MIC, AUC, and AUC/MIC have a role as surrogates in predicting the efficacy of beta lactams?

Both T>MIC and AUC (AUIC) are predictive of bacteriologic outcome for time-dependent-killing antimicrobial agents and the dosing interval may affect the role of T>MIC as the major surrogate for efficacy (Schentag, J et al., Clin Infect Dis, 1998). In addition, covariance may play a role in the models of peak MIC, T>MIC and AUC/MIC, and in the interpretation of these surrogates for beta-lactams (Hyatt JM et al., Clin Pharmacokinetics, 1995).

4. Protein binding

The concentration of unbound drug in the fluid of the infected tissue should be used to predict the antibacterial efficacy of a drug because only the unbound fraction of a drug can influence the PK parameter, and only the free fraction of the drug is effective against microorganisms (Cars, O. Diagn Microbiol Infect Dis, 1997). Neither total blood

concentrations nor total tissue concentrations are good predictors of clinical efficacy (Scaglione F. Ped Inf Dis J. 1997). Therefore, T>MIC in the middle ear fluid should be the preferred indicator for bacteriologic efficacy in AOM (Canafax D et al., Pediatr Infect Dis J 1998). There are no data in the application on T>MIC in the MEF for Augmentin 90mg/kg/day.

5. Antibiotic concentrations in the middle ear

Middle ear fluid concentrations can vary with the degree of protein binding, the presence of a concurrent viral infection, contamination with blood (which can occur during tympanocentesis), the variability in gastrointestinal absorption of beta-lactams, patient differences in the antibiotic penetration rates into the middle ear, and the rate of clearance of MEF (Harrison C. Pediatr Infect Dis J, 1997). For example Canafax et al., (Pediatr Infect Dis J, 1998) found that MEF amoxicillin concentrations from the left and right ears of 6/7 evaluable patients differed by about 2 fold.

Protocol 25000/447

Title: "A comparison of the safety and efficacy of Augmentin 90/6.4mg/kg/day q12 hours and Augmentin 45/6.4mg/kg/day q12 hours in the treatment of acute otitis media in children"

Primary Objective

The primary objective of the study was to compare the incidence of adverse experiences, particularly lower gastrointestinal disturbances that satisfy the criteria of protocol-defined diarrhea, in children receiving Augmentin 90/6.4 mg/kg/day administered every 12 hours with food for 10 days versus Augmentin 45/6.4 mg/kg/day, administered every 12 hours with food for 10 days.

Secondary Objective

A secondary objective of this study was to compare the clinical efficacy of q 12 hrs Augmentin 90/6.4 mg/kg/day versus q 12 hrs *Augmentin* 45/6.4 mg/kg/day each administered for 10 days in the treatment of acute otitis media in children.

Treatment and Administration

Patients meeting the study entry criteria were randomized equally (1:1 ratio) to one of two treatment groups:

Group A: Augmentin 90/6.4 mg/kg/day every 12 hours with food for 10 days OR

Group B: Augmentin 45/6.4 mg/kg/day every 12 hours with food for 10 days.

Prior and Concomitant Medications

During the trial, concomitant medication(s) necessary for the health of the patient were permitted; however, no additional antimicrobial therapy (except for ophthalmic or other topical antibiotics) was allowed. Patients who received alternate antibiotics because of no improvement, worsening, or recurrence of signs and symptoms of AOM were, by definition, "clinical failures" at EOT or "recurrences" at FU. Medications with the potential to alter bowel habit were to be avoided during the study period.

Concomitant use of oral or nasal antihistamines, decongestants, antifungals and/or steroids was permitted during the course of the study. Tubular secretion inhibitors of Augmentin (*e.g.*, probenecid) were prohibited.

Medical Reviewer's comments:

Based on the IDSA guidelines, the use of decongestants and antihistamines should be discouraged, and if used, should be recorded. Since it appears that the use of adjunctive therapies other than steroids has little influence on the resolution and outcome of AOM, the reviewer will accept patients who received these therapies for evaluability.

STUDY POPULATION

Number of Patients

Patients were enrolled without regard to sex, race, or socioeconomic status. It was anticipated that approximately 450 patients would be enrolled into the study to provide 380 evaluable patients in up to 25 centers. No one center could contribute more than 40% of the evaluable patients.

Inclusion Criteria

A patient may be included in this study, if the patient:

- is 3 months to 12 years of age,
- is able to comply with the protocol,
- has *acute otitis media*, diagnosed on the basis of otoscopic findings as defined below:
  a. Purulent otorrhea of less than 24 hrs duration

  OR

  b. Middle ear effusion

  Middle ear effusion is evidenced by at least two of the following:
  1. decreased or absent tympanic mobility measured by pneumatic otoscopy,
  2. yellow or white discoloration of the tympanic membrane, or
  3. opacification of the tympanic membrane.

  Plus

  at least one of the following indicators of acute inflammation:
  1. ear pain within 24 hours, including unaccustomed tugging or rubbing of ear,
  2. marked redness of the tympanic membrane, or
  3. distinct fullness or bulging of the tympanic membrane.
- has written informed consent from a parent or legal guardian.

The investigator made a clinical diagnosis of AOM using otoscopic findings of either purulent otorrhea or MEE with acute inflammation.
Before entering a patient with signs and symptoms of AOM into the study, the investigator was to specifically evaluate and grade the following signs and symptoms of infection accordingly:

Specific Symptoms of Acute Otitis Media

Otalgia (within 24 hrs): yes (*e.g.*, unaccustomed tugging or rubbing of ear)
no, or unable to evaluate

Non-Specific Symptoms of Acute Otitis Media

Fever (oral or tympanic/oral temperature):
moderate to severe (>101°F)
mild (99.5°F - 101°F), or
none (<99.5°F), or
equivalent rectal or tympanic/rectal (stated values + 1°F), or
axillary (stated values - 1°F) temperatures.

Irritability: yes or no
Loss of appetite: marked, moderate, or none
Rhinorrhea: yes or no

Otoscopic Findings

Otorrhea: purulent, serous, or none
Middle ear effusion: yes or no

Examination of Tympanic Membrane

Tympanic membrane (TM): perforated or intact

TM mobility: absent, decreased, or normal
TM color: opaque (markedly erythematous), yellow-white, or normally translucent
TM position: bulging (*i.e.*, distinct fullness), retracted, or neutral

Medical reviewer's comments:
The reviewer considered the presence of following findings to be consistent with acute otitis media:

1. distinct swelling or bulging of the tympanic membrane
2. decreased or absent tympanic mobility measured by pneumatic otoscopy
3. opacification of the tympanic membrane, and
4. erythematous, yellow or white discoloration of the tympanic membrane.

The following findings was considered supportive of the diagnosis of AOM when present: ear pain within 24 hours, including unaccustomed tugging or rubbing of ear, generalized redness of the tympanic membrane, fever, irritability, decreased hearing, or purulent otorrhea. Hyperemia or redness of the TM alone or ear pulling, alone were not adequate for the diagnosis of AOM.

Exclusion Criteria
A patient will be excluded if:

- weighs more than 40 kg;
- has spontaneous perforation of the tympanic membrane and drainage for longer than 24 hours;
- has tympanoplastic tube(s) in place, or has anatomic abnormalities associated with prolonged middle ear effusion, including cleft palate or repair, high-arched palate or Down's syndrome;
- has a concomitant infection;
- has known renal insufficiency (*e.g.*, plasma creatinine ≥ 1.5 times upper limit of normal range for age);
- has a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction;
- has phenylketonuria or a known hypersensitivity to aspartame;
- has received within 48 hours of study entry, or is scheduled to receive during the study period, any medication which may alter bowel function;
- is currently receiving or has received more than one dose of systemic antibiotic therapy within one week prior to the initiation of the study (with the exception of patients who have developed acute otitis media while taking antimicrobial prophylactic therapy with either amoxicillin, erythromycin, sulfizoxazole, or trimethoprim-sulfamethoxazole).

Medical reviewer's comments:
The reviewer agrees with the applicant's criteria for exclusion with the exception of the inclusion of patients on prophylactic medications. The reviewer considered these patients non-evaluable.

EVALUATION VISITS
On-Therapy
Clinical Status at the On-Therapy Telephone Visit
An on-therapy telephone assessment on study days 3 to 5 was required after two full days (4 doses) of study medication. If the condition of the patient had not improved or worsened by the

on-therapy telephone contact, then an *interim visit* was required within 24 hrs of the contact to determine if the patient was to be withdrawn from or continued in the study.

Medical Reviewers' comments:
Divisional Guidelines recommend that patients who are not adequately responding to at least 3 days of study therapy should undergo tympanocentesis to document the unresponsive pathogen.

End of Therapy Evaluation--EOT (Days 12 to 14)
Patients continuing in the study were to return for a scheduled end of therapy evaluation on days 12 to 14.

Medical Reviewer's comments:
The applicant based the final clinical outcome on the results of this visit. This is, however, not the test-of-cure visit (TOC) for the reviewer.

Follow-Up Evaluation (Days 22 to 28)
All patients (including withdrawals) returned either for a scheduled follow-up visit on days 22 to 28 or earlier if symptoms recur. Patients with recurrence of symptoms of acute otitis media prior to the follow-up visit (days 22 to 28) were required to return to the office at the time of recurrence, in place of the scheduled post-therapy follow-up assessment. Early failures or withdrawals were to be assessed at the time of failure (interim visit); later failures were to be assessed at EOT and also at the time of failure/withdrawal *(i.e.,* early FU assessment). Signs and symptoms were not recorded for patients who received additional antibiotics as these patients are unevaluable for their response to *Augmentin* at follow-up.
Overall compliance with the study medication schedule between 80% and 120% (and intake of at least four doses on days 1 and 2) was required for the patient to be considered evaluable per protocol.

Medical Reviewer's comments:
This is the TOC visit for the reviewer.

Efficacy Analyses
Primary Efficacy Parameter
The primary efficacy endpoint was clinical response at EOT on days 12 to 14. The primary efficacy analysis was performed on both the intent to treat (ITT) and the per protocol (PP) population at EOT. A treatment success was defined as either "clinical cure" or "improvement" at EOT.

Evaluation of Clinical Response at the End of Therapy (Days 12 to 14) or Interim Visit
The investigator evaluated each patient's clinical outcome as follows:
Clinical Cure: complete resolution of specific symptoms of AOM and otoscopic signs of acute infection with inflammation, with or without middle ear effusion, MEE, such that no additional antibiotic therapy was required for acute otitis media, AOM.

Improvement: improvement, but incomplete resolution of specific symptoms of acute otitis media and/or otoscopic signs of acute infection with inflammation, with or without middle ear effusion, such that no additional antibiotic therapy is prescribed for acute otitis media.

Clinical Failure: inability to clear or improve the otoscopic signs of acute infection with inflammation and specific symptoms of acute otitis media after two or more days of therapy. Additional antibiotic therapy is prescribed for acute otitis media.

OUTLINE OF STUDY PROCEDURES

(modified from applicant's version)

	Days -1 to 0 Preliminary Visit[a]	Days 3 to 5 On-Therapy Telephone Call[b]	Interim Visit[c]	Days 12 to 14 End of Therapy Visit[d]	Days 22 to 28 Follow-up Visit[e]
Written Dated Informed Consent	X				
Medical History	X				
Physical Examination	X				
Ear Examination	X		X	X	X
Clinical Assessment	X	X	X	X	X
Call to ClinPhone®	X*		X**	X	X
Baseline Signs and Symptoms	X				
Adverse Experiences		X	X	X	X
PriorConcomitant Medication	X	X	X	X	X
Review of Diary Card	X		X	X	
Assessment of Compliance		X		X	
					x

[a] Within 24 hrs of notification (required only if symptoms worsen, do not improve, or recur)

* If patient is randomized

**If patient is withdrawn from study

Medical Reviewer's comments:

Reviewer agrees with visits as planned and notes that the timing of the visits is consistent with the IDSA guidelines. The reviewer's test of cure visit is the follow-up visit on days 22-28.

Unable to Determine: A valid assessment of clinical outcome could not be made (*e.g.*, the patient did not attend visit or consent to clinical examination, or less than two days of medication were taken).

Secondary Efficacy Parameter
The secondary efficacy endpoints were recurrence at follow-up and global clinical response. Clinical efficacy assessments were performed at follow-up only for patients who were treatment successes at the end of therapy.

Evaluation of Clinical Response at Follow-Up (Days 22 to 28)
Persistent Clinical Cure: resolution of specific symptoms and otoscopic signs of acute infection for those patients who were clinically cured or improved at the end of therapy such that no additional antibiotic therapy was prescribed for acute otitis media.

Clinical Recurrence: reappearance of otoscopic signs and specific symptoms of acute infection for those patients who were clinically cured or improved at the end of therapy. Additional antibiotic therapy was required for acute otitis media.

Unable to Determine: a valid assessment of clinical outcome could not be made (*e.g.*, the patient did not attend a visit, or extenuating circumstances).

Medical reviewer's comments:
Failures from the end of therapy visit were not carried forward to the end of study visit by the applicant; these failures were carried forward by the reviewer and included in the reviewer's analysis of outcome at the final visit.

Global Clinical Response
Global Clinical Response is a secondary efficacy variable and defined as:
Success - Patient classified as clinical outcome of "Clinical Cure" or "Improvement" at end-of-therapy and did not experience a recurrence of the infection by the follow-up visit.

Failure - Patient who failed to respond to therapy, withdrew from the study, or experienced a recurrence of acute otitis media before or at the follow-up visit.

Definitions of clinical response were as shown below:

End of Therapy	Follow-Up	Global Clinical Response
Cure/Improvement	Persistent Clinical Cure	Success
Cure/Improvement	Clinical Recurrence	Failure
Cure/Improvement	Unable to Determine	Failure
Clinical Failure	NA	Failure
Unable to Determine	NA	Failure

Patient Completion and Withdrawal
Patients would have completed the study if they satisfied all study entry criteria, completed the 10-day double-blind phase of the study and returned for the end of therapy (days 12 to 14) and follow-up (days 22 to 28) visits. A *withdrawal* was any patient who entered the study (*i.e.*, gave informed consent *and was randomized*), but did not complete the study (whether or not the patient received study medication).

Medical reviewer's comments:
Any patients removed from the study prematurely for insufficient therapeutic effect (i.e., failure) after 3 days of therapy was considered evaluable.

Applicant's Evaluability criteria for clinical efficacy (Criteria for Inclusion in the Per Protocol Efficacy Analyses)

1. clinical diagnosis of acute otitis media as defined in this protocol.
2. compliance of between 80 and 120% with the prescribed medication, and intake of at least 4 doses on days 1 and 2. If completed the study, compliance must have been at least 16 doses of study medication. A patient who withdrew due to clinical failure before completing the study must have taken a minimum of 48 hours of therapy (i.e., four doses of study medication) to be evaluable.
3. patient did not receive any prohibited medication.
4. patient evaluated at the appropriate follow-up visits.

Medical Reviewer's efficacy evaluability criteria

Regarding the applicant's criteria:

1. The medical officer agrees with the applicant that patients were evaluable only if they met the clinical diagnosis of AOM; however, the reviewer used Divisional criteria for the diagnosis of AOM.
2. The definition of the minimum duration of therapy needed for evaluability used by the reviewer was at least 6 doses of study drug. In addition, patients could not have missed more than two consecutive doses or received between 80-120% of study drug [patients withdrawn for adverse event before receiving 8 days or 16 doses of therapy were not evaluable for efficacy (but were evaluable for safety)].
3. and 4. The reviewer agrees with these criteria. However, the reviewer used the end of study visit as the TOC visit.

Additionally, the reviewer considered patients evaluable if:

- enrollment criteria were met
- not treated with any systemic antimicrobial agents within 7 days of study enrollment, including antimicrobial prophylaxis
- did not receive adjunctive medications such as steroids (oral steroids within 24 hours of study or injection of other steroids within 30 days)
- not withdrawn or lost to follow-up before the end of study, except for clinical failure
- did not have otorrhea/perforation of TM
- had at least 7 days between completion of therapy and the follow-up (test-of-cure) visit

Subset analyses were planned for patients meeting the following criteria:

- recurrent or chronic otitis media defined as 4 or more distinct episodes in the past 12 month period, or 3 or more episodes in the last 6 months
- history of acute OM within 30 days of study entry

Clinical failures were defined as follows:

- use of additional systemic antimicrobial agents to treat otitis media, or intercurrent illness related to AOM, between study initiation and the end of the study visit required
- patients with continuing symptoms (insufficient therapeutic response) after 6 consecutive doses of study therapy (failures at any time after 3 days of therapy up to the end of the study were considered failures at the final visit outcome) as long as the other evaluability criteria were met.

Differences in the criteria for the diagnosis of AOM, definitions of clinical evaluability, and the definitions of the test-of-cure were expected to contribute to differences in the numbers of evaluable patients between the applicant and the reviewer.

Efficacy Analysis
Statistical Methods
Comparison of efficacy is secondary. The primary efficacy endpoint is the clinical response of a patient at the end-of-therapy. Two-sided 95% confidence intervals will be used to evaluate the differences in the proportion of patients who were treatment successes.
The comparison of primary interest is incidence of protocol-defined diarrhea (PDD) as a measure of tolerance. Assuming an underlying equivalent PDD response rate of 10%, 190 patients per treatment arm (380 total) would be required to give a 90% power to detect that the upper bound of the two-sided 95% confidence interval for the difference in rates (90 mg group minus 45 mg group) is no more than 10%.

Medical reviewer's comments:
See statistical review by Li Ming Dong, Ph.D.

Bowel Habit Analyses
Two-sided 95% confidence intervals will be used to evaluate the differences between treatment groups in the rate of PDD. If there are sufficient numbers of patients per center, the treatment by center interaction effects will be examined.

Bowel Habit Evaluable Population
(i) Per Protocol Bowel Habit Population
This population will provide the primary analysis.
The following two criteria must have been met for the patient to be included in the per protocol bowel habit population:
- At least 80% but no more than 120% compliance with study medication
- Patient has not received medication that may alter bowel function within 48 hours of entering the study or during the study.

(ii) Intent-to-Treat Population
All randomized patients who took at least one dose of study medication. Patients will only be excluded from this population if they took no study medication.

Safety Assessments
Bowel Habits
Tolerability
The primary bowel habit variables were incidence and characteristics of bowel movements, including PDD; secondary bowel habit variables were consistency and frequency of bowel movements. Bowel habit data were collected for each patient using Patient Diary cards; PDD was summarized on a daily basis for patients in each treatment group.
For this study, protocol-defined diarrhea is:
- three or more *watery* stools in one day OR
- two *watery* stools per day for two consecutive days.

Stool consistency will be described as having one of the following forms:
- *Hard* - small, pellet-like;
- *Well-Formed* - retains its shape;
- *Semi-Formed* - soft stools that retain some form;
- *Loose* - very soft/sloppy stools; or
- *Watery* - mainly water that may have some formed particles.

An additional definition of diarrhea was also assessed as a safety measure. This was defined as:
- 3 or more watery stools in one day OR

- 4 or more loose/watery stools in one day OR
- 2 watery stools per day for two consecutive days OR
- 3 loose/watery stools per day for two consecutive days.

Patients who withdrew due to diarrhea or had a documented SAE of diarrhea were considered to have fulfilled the criteria for PDD and were analyzed as such, even in the absence of diary card data.

Adverse Experiences

Baseline signs or symptoms were elicited by asking ***"Has your child felt different in any way in the last 7 days?"*** AEs were elicited at each assessment by the investigator asking the patients/parents/guardians ***"Do you or does your child feel different in any way since starting the treatment or since the last visit?"***

Serious AEs (SAE) which occurred during the study or within 30 days of receiving study medication, whether or not related to study medication, were reported by the investigator to the medical monitor by telephone within 24 hours. Any instance of overdosage (suspected or confirmed) was documented as an SAE.

No laboratory tests were required.

Pharmacokinetic, Pharmacodynamic, and Pharmacoeconomic Assessments

No pharmacokinetic, pharmacodynamic or pharmacoeconomic assessments were included in this study.

SUMMARY OF STUDY DESIGN, Study 25000/447

Primary Objective	to compare the incidence of adverse experiences
Secondary Objective	to compare the clinical efficacy of *Augmentin* 90/6.4 mg/kg/day q12h vs. *Augmentin* 45/6.4 mg/kg/day q12h
Study design	Randomized, double blind, multicenter, comparative study
Study dates	11 December 1996-27 February 1997
Patients Population	males and females; 3 months to 12 years
Location	US; 18 sites
Study drug dosing	*Augmentin* 90/6.4 mg/kg/day every 12 hours
Comparator	*Augmentin* 45/6.4 mg/kg/day every 12 hours
Duration of therapy	10 days
Inclusion Criteria	Purulent otorrhea of less than 24 hrs duration OR Middle ear effusion Middle ear effusion is evidenced by at least two of the following: 1. decreased or absent tympanic mobility measured by pneumatic otoscopy, 2. yellow or white discoloration of the tympanic membrane, or 3. opacification of the tympanic membrane. plus at least one of the following indicators of acute inflammation: 1.ear pain within 24 hours, including unaccustomed tugging or rubbing of ear, 2.marked redness of the tympanic membrane, or 3.distinct fullness or bulging of the tympanic membrane.
Exclusion Criteria	has spontaneous perforation of the tympanic membrane and

	drainage for longer than 24 hours; has tympanoplastic tube(s) in place, or has anatomic abnormalities associated with prolonged middle ear effusion
Evaluation visits	Baseline Telephone evaluation days 3-5 Interim On therapy as needed End of therapy days 12-14 End of study days 22-28
Randomized	202/209; 3 did not receive study drug
MO Evaluability Criteria	• clinical diagnosis of AOM based on Divisional criteria • at least 6 doses of study therapy • the TOC visit was the follow-up (EOS) visit • no systemic antimicrobial agents within 7 days of study enrollment, including antimicrobial prophylactic agents • received between 80-120% of study drug [patients withdrawn for adverse event before receiving 8 days or 16 doses of therapy were not evaluable for efficacy] • no adjunctive steroids (oral steroids within 24 hours of study or injection of other steroids within 30 days) • not withdrawn or lost to follow-up before EOS, except for clinical failure • no otorrhea/perforation of TM • at least 7 days between completion of therapy and EOS visit Clinical failures: • additional systemic antimicrobial agents to treat acute otitis media or intercurrent illness related to AOM between study initiation and EOS • insufficient therapeutic response after 6 consecutive doses of study therapy (failures at any time after 3 days of therapy to EOS visit were carried forward to the final visit outcome) Patients meeting the following conditions will be evaluated as a subset: recurrent or chronic otitis media defined as 4 or more distinct episodes in the past 12 month period, or 3 or more episodes in the last 6 months
MO evaluable at EOS	116/120
Sponsor evaluable at EOS	161/159
Primary Efficacy Parameter	clinical response rate at EOS

RESULTS

Study Dates

The first patient was enrolled on 11 December 1996 and the last study visit was 27 February 1997.

Principal investigators, affiliated institutions, and clinical study site locations

Site#	Principal Investigator	Affiliated Institution	City, State, Country
001	Gerald W. Bottenfield, MD	RD Clinical Research, Inc.	Lake Jackson, TX
002	Robert A. Fiddes, MD	SCRI, Inc.	Whittier, CA
003	Fred M. Jorgensen, MD	Fairview Hospital	Cleveland, OH
004	Anthony D. Puopolo, MD	Milford Emergency Assoc., Inc.	Olympia, WA
005	Robin L. Schaten, MD	Longmont Clinic, PC	Longmont, CO
006	Shelly D. Senders, MD	(private practice)	Univ. Heights, OH
007	Cameron A. Shearer, MD	West Wilson Family Practice	Mt. Juliet, TN
008	Malcolm J. Sperling, MD	Fountain Valley Regional Hosp.	Fountain Valley, CA
009	Alejandro Hoberman, MD	Children's Hospital of Pittsburgh	Pittsburgh, PA
010	Gerson H. Aronovitz, MD	(private practice)	Atlanta, GA
011	Jeffrey Barter, MD	Littleton Pediatric Med. Center	Littleton, CO
012	Jeffrey Adelglass, MD	Research Across America	Dallas, TX
013	Douglas A. Eisert, MD	Wenatchee Valley Clinic	Wenatchee, WA
014	Robert A. Maxwell, MD	(private practice)	Shawnee Mission, KS
015	James A. Hedrick, MD	Physicians to Children & Adol., PSC	Bardstown, KY
016	Robert Zorba Paster, MD	Dean Medical Center	Oregon, WI
017	Stephen A. Chartrand, MD	Creighton Pediatrics, Infect. Dis.	Omaha, NE
018	Jeffrey L. Blumer, MD	Rainbow Babies & Children's Hosp.	Cleveland, OH
019	Christopher Thoming, MD	Good Samaritan Hosp. & Med. Ctr	Portland, OR
020	Samuel Licata, MD	PA State University Children's Hosp.	Hershey, PA

- Site 019 was initiated too late to participate in patient enrollment

Medical Reviewer's comments:

Twenty centers were planned for participation in the study; the results which follow reflect the involvement of 18 centers, since one center did not enroll patients, and the investigator at center 002 was disqualified.

The 18 sites are distributed across the United States. Excluding site 002, there were 2 Northeastern sites, 3 sites in the Southeast, 5 sites in the west, 6 sites in the Midwest and 2 Southwestern sites; this distribution is accepted as being representative of the population.

Four hundred and eleven case report forms (excluding patients from study center 002) were reviewed for evaluability and safety, without knowledge of the treatment arm assignment of the patients.

Documentation of the number of distinct and well documented episodes of AOM in the previous 12 months, and the history of recurrent or chronic acute otitis media was inconsistent among the investigators. In addition to the poor documentation of previous episodes of AOM at site 001, the use of prior systemic antimicrobial agents by patients was also incompletely documented.

The diagnosis of AOM vs. MEE for patients with similar presentations was inconsistent among investigators at the follow-up visit. These differences in the diagnosis affected the assignment of outcome and the assessment of efficacy.

PATIENT ENROLLMENT AND DISPOSITION

Sponsor Table of Number Of Patients Randomized, Completing, And Valid For ITT Bowel Habit Analysis By Center, Intent-To-Treat Population

			Treatment Group					
			Augmentin-90			Augmentin-45		
Center	Investigator	Site	R	C	V	R	C	V
001	Bottenfield	Lake Jackson, TX	44	41	44	46	43	46
003	Jorgensen	Cleveland, OH	1	0	0	1	1	1
004	Puopolo	Milford, MA	8	6	8	8	8	8
005	Schaten	Longmont, CO	18	16	16	18	18	18
006	Senders	University Heights, OH	17	15	17	17	15	17
007	Shearer	Mt. Juliet, TN	1	1	1	1	1	1
008	Sperling	Fountain Valley, CA	16	16	16	17	14	17
009	Hoberman	Pittsburgh, PA	22	22	22	23	21	21
010	Aronovitz	Atlanta, GA	5	5	5	5	5	5
011	Barter	Littleton, CO	14	12	14	14	14	14
012	Adelglass	Dallas, TX	6	5	6	7	5	6
013	Eisert	Wenatchee, WA	4	3	4	4	4	4
014	Maxwell	Mission, KS	6	5	6	6	6	6
015	Hedrick	Bardstown, KY	22	20	21	23	22	23
016	Paster	Oregon, WI	4	3	4	4	2	4
017	Chartrand	Omaha, NE	2	2	2	2	2	2
018	Blumer	Cleveland, OH	10	4	10	10	7	9
020	Licata	Hershey, PA	1	1	1	1	1	1

Total Number Of Patients	201	176	197	207	189	203

R = Randomized, C = Completed (Satisfied all study entry criteria, completed the 10 day on-therapy phase of the study, and attended the End of Therapy and Follow-up visits), V = Valid for Intent-to-Treat bowel habit population. Augmentin-90 = 90/6.4 mg/kg/day Augmentin (q 12 hr, 10 days), Augmentin-45 = 45/6.4 mg/kg/day Augmentin (q 12 hr, 10 days).

Medical Reviewer's comments:

This sponsor table was modified to remove patients from center 002 and the totals adjusted accordingly. Four hundred and eleven patients were randomized into the study, 202 into the Augmentin-90 arm, and 209 into the Augmentin-45 arm. This modified sponsor table indicates that 201 and 207 patients were randomized to the Augmentin-90 and Augmentin-45 treatment arms respectively; however this table does not account for 3 patients who were randomized, but did not receive study drug. Patient 008-465, randomized to the Augmentin-90 treatment arm, did not receive study drug because the consent was withdrawn after randomization. Therefore, of 202 patients randomized to the Augmentin-90 study arm, 201 received study drug. Patient 001-53, randomized to the Augmentin-45 arm did not receive study drug because the sponsor ran out of study drug. Patient 014-345 was incorrectly randomized to the Augmentin-45 arm without documented informed consent; the patient was withdrawn before the administration of any study medication.

Center 001 accounted for 22% of the patients randomized into the trial. Two other centers, 009 and 015, each accounted for approximately 11% of the patients in the trial with more than 20 patients randomized per arm.

MO Table Patients evaluable by center, based on MO evaluable population

		Augmentin 90			Augmentin 45		
center ID	total randomized	enrolled	evaluable	% evaluable	enrolled	evaluable	% evaluable
001	91	44	22	50	46	20	43.5
003	2	1	0	0	1	0	0
004	16	8	0	0	8	2	25
005	36	18	11	61	18	12	66.7
006	34	17	12	70.6	17	11	64.7
007	2	1	1	100	1	0	0
008	33	16	11	68.8	17	11	64.7
009	45	22	18	81.8	23	15	65.2
010	10	5	4	80	5	4	80
011	28	14	10	71.4	14	11	78.6
012	13	6	4	66.7	7	4	57.1
013	8	4	3	75	4	2	50
014	12	6	2	33.3	6	5	83.3
015	45	22	13	59.1	23	15	65.2
016	8	4	2	50	4	2	50
017	4	2	1	50	2	1	50
018	20	10	2	20	10	4	40
020	2	1	0	0	1	1	100
Total	411	201	116	57.7	207	120	58.0

Medical Reviewer's comments:
Patients considered enrolled in the study were those who received at least one dose of study drug, excluding the 3 patients (discussed above) who did not receive study drug.
Three centers, 001, 009, and 015, contributed 20 or more patients per arm to the total number of randomized patients; each accounted for 10% of the evaluable patients. Although 22% of the patients in the clinical trial were enrolled at site 001, the proportion of evaluable patients out of the total from this center was about 10%. Fifty percent and 43.5% of the patients in the Augmentin-90 and Augmentin-45 treatment arms, respectively were unevaluable because, based on the reviewer's criteria, the baseline diagnosis in these patients was MEE and not AOM. In the centers with larger enrollments, the proportion of evaluable patients in each treatment arm was comparable except at site 009 where more patients were evaluable in the Augmentin-90 arm. Only two of the 16 patients enrolled at site 004 were evaluable. Overall, equal proportions of patients were evaluable in each study arm.

Sponsor Table
Listing of Patient Withdrawals, excluding patients from center 002

Patient Number	Completed Study	Date Withdrawn	Reason For Withdrawal	Comments
Augmentin-90 N=25				
447.001.00391	No	17JAN1997	Insufficient Therapeutic Effect	
447.001.00584	No	28JAN1997	Insufficient Therapeutic Effect	
447.001.00598	No	29JAN1997	Insufficient Therapeutic Effect	
447.003.00002	No	13JAN1997	Adverse Experience	
447.004.00131	No	30JAN1997	Other	NO INTERIM VISIT.SAW PRIMARY MD-30JAN97 FOR WHEEZING.STARTED ZITHROMAX PER MD
447.004.00133	No	04FEB1997	Adverse Experience	
447.005.00483	No	20JAN1997	Lost To Follow-Up	
447.005.00489	No	22JAN1997	Other	MOTHER SIGNED CONSENT - FATHER REFUSED PERMISSION AFTER MOTHER GOT HOME.
447.006.00157	No	22JAN1997	Protocol Deviation, Including Non-Compliance	
447.006.00370	No	31JAN1997	Protocol Deviation, Including Non-Compliance	
447.008.00465	No	20JAN1997	Other	
447.011.00221	No	09JAN1997	Adverse Experience	WITHDREW CONSENT; NO STUDY DRUG GIVEN
447.011.00229	No	17JAN1997	Insufficient Therapeutic Effect	
447.012.00288	No	06FEB1997	Lost To Follow-Up	
447.013.00306	No	11FEB1997	Protocol Deviation, Including Non-Compliance	
447.014.00352	No	05FEB1997	Adverse Experience	
447.015.00324	No	21JAN1997	Adverse Experience	
447.015.00334	No	15JAN1997	Adverse Experience	
447.016.00187	No	27JAN1997	Adverse Experience	
447.018.00441	No	22JAN1997	Protocol Deviation, Including Non-Compliance	
447.018.00444	No	04FEB1997	Other	REQUIRED ADDITIONAL ANTIBIOTICS FOR NEW INFECTION OTHER THAN OTITIS MEDIA
447.018.00451	No	27JAN1997	Other	CHILD REFUSING TO TAKE MEDICATION
447.018.00454	No	05FEB1997	Protocol Deviation, Including Non-Compliance	
447.018.00456	No	12FEB1997	Protocol Deviation, Including Non-Compliance	
447.018.00460	No	13FEB1997	Protocol Deviation, Including Non-Compliance	

Augmentin-45 N=20

447.001.00051	No	07JAN1997	Protocol Deviation, Including Non-Compliance	
447.001.00053	No	26DEC1996	Other	SPONSOR RAN OUT OF DRUG; NO STUDY DRUG GIVEN
447.001.00400	No	21JAN1997	Insufficient Therapeutic Effect	
447.001.00599	No	28JAN1997	Adverse Experience	
447.006.00372	No	12FEB1997	Protocol Deviation, Including Non-Compliance	
447.006.00374	No	04FEB1997	Protocol Deviation, Including Non-Compliance	REFUSAL TO TAKE DRUG
447.008.00177	No	17JAN1997	Other	CHILD WOULD NOT TAKE MEDICATION MOTHER WITHDREW CONSENT ONE DOSE OF STUDY DRUG GIVEN
447.008.00466	No	23JAN1997	Other	
447.008.00472	No	31JAN1997	Insufficient Therapeutic Effect	PATIENT WOULD NOT TAKE THE MEDICATION
447.009.00034	No	06JAN1997	Lost To Follow-Up	
447.009.00202	No	31JAN1997	Protocol Deviation, Including Non-Compliance	
447.012.00286	No	23JAN1997	Adverse Experience	
447.012.00292	No	14FEB1997	Lost To Follow-Up	
447.014.00345	No	24JAN1997	Other	PATIENT INCORRECTLY RANDOMIZED WITHOUT INFORMED CONSENT; NO STUDY DRUG GIVEN
447.015.00332	No	15JAN1997	Adverse Experience	
447.016.00182	No	17JAN1997	Adverse Experience	
447.016.00183	No	18JAN1997	Protocol Deviation, Including Non-Compliance	
447.018.00442	No	24JAN1997	Lost To Follow-Up	
447.018.00447	No	04FEB1997	Protocol Deviation, Including Non-Compliance	
447.018.00452	No	05FEB1997	Protocol Deviation, Including Non-Compliance	

Source: Listing B2 from NDA submission

Medical reviewer's comment:
Note that the table includes the 3 patients withdrawn before the initiation of study drug.

Sponsor Table Patient Disposition By Treatment Group, excluding site 002

	Treatment Group	
	Augmentin-90	Augmentin-45
Randomized	202	209
Evaluated For Intent-To-Treat	202	209
Completed Study	177	189
Withdrawn	24	18
Evaluated For Safety	201	207
Adverse events	101	98

Medical reviewer's comments:
The total number of withdrawals differs from that in the previous table. In the calculation of the number withdrawn in the tables on this page, the sponsor has not included the 3 patients (see patient withdrawals listing) who were withdrawn before receiving study drug. Note, however, that these 3 patients (1 in the Augmentin-90 arm and 2 in the Augmentin-45 arm) are included in the totals for randomized , ITT, and total number of patients in these tables.

Sponsor Table Patient Withdrawals
Intent-To-Treat Population, excluding site 002

	Treatment Group			
	Augmentin-90		Augmentin-45	
	N	%	N	%
Number Of Patients Who Completed Study	177	87.6	189	90.4
Adverse Experience	7	3.5	4	1.9
Insufficient Therapeutic Effect	4	2.0	2	1.0
Protocol Deviation, Including Non-Compliance	7	3.5	7	3.3

Lost To Follow-Up	2	1.0	3	1.4
Other*	4	2.0	2	1.0
Total Number Of Patients Withdrawn	24	11.9	18	8.6
Total Number Of Patients	202	100.0	209	100.0

* The reasons for withdrawal included consent withdrawn, refusal to take medication, additional antimicrobial agents for new infection other than AOM, and another antimicrobial prescribed by non-investigator physician.

Medical reviewer's comments:
More patients were withdrawn from the Augmentin-90 arm; differences in the rates of adverse events in the two groups accounted for most of the of the difference in the number of withdrawals. Almost twice as many patients were withdrawn for adverse events in this treatment arm, however, the numbers are too small for any generalizations to be made.

MO Table Reasons for Clinical Non Evaluability, excluding patients from center 002

	Augmentin-90 n (%)	Augmentin-45 n (%)	Total n
No. of patients	202	209	411
No. of patients excluded	86 (42.6)	89 (42.6)	175
no AOM diagnosis	47 (23.3)	47 (22.5)	94
perforation and/or otorrhea	12 (5.9)	12 (5.7)	24
prior antimicrobial w/in 1wk of study	8 (4.0)	9 (4.3)	17
concomitant antimicrobial	5 (2.5)	5 (2.4)	10
insufficient (<6 doses) or no therapy	2 (1.0)	5 (2.4)	7
lost to follow-up	6 (3.0)	3 (1.4)	9
adverse drug reaction	3 (1.5)	4 (1.9)	7
consent not obtained or withdrawn	2 (1.0)	2 (1.0)	4
no patient diary returned	0	2 (1.0)	2
missed 4 or more consecutive doses	1 (0.5)	0	1
No. of evaluable patients	116 (57.4)	120 (57.4)	236

Medical reviewer's comments:
Patients were assessed for evaluability without knowledge of treatment arm assignment (i.e., blinded assessment). Because of differences in the diagnostic criteria and the definitions of primary efficacy, the number of patients excluded by the applicant and the reviewer differed. Those patients who had more than one reason for non-evaluability are accounted for only once in this table. Approximately forty three (42.6)% of the patients in each treatment arm were excluded by the reviewer, the majority for diagnosis not consistent with AOM.

DEMOGRAPHICS and DISEASE CHARACTERISTICS

MO Table Demographic characteristics (excluding site 2) of Sponsor's randomized population

Demographic Characteristics	Augmentin-90		Augmentin-45	
	n	(%)	n	(%)
Age				
<6 mo	6	(3.0)	13	(6.2)
> 6 mo and < 2 yr	82	(40.6)	74	(35.4)
≥2 and < 5 yr	69	(34.2)	74	(35.4)
≥ 5 yr and < 8 yr	27	(13.4)	38	(18.2)
≥ 8 yr and < 12 yr	18	(8.9)	10	(4.8)
Mean [SD] (years)	3.14 [2.63]		3.18 [2.47]	
Minimum (years)	0.25		0.25	
Maximum (years)	11.67		11.33	
Weight (kg)				
Mean [SD]	15.09 [6.69]		15.04 [6.56]	
Minimum	6.0		6.0	
Maximum	40.0		39.7	
Gender				
Female	98	(48.5)	92	(44.0)
Male	104	(51.5)	117	(56.0)
Race				
White	158	(78.2)	168	(80.4)
Black	18	(8.9)	22	(10.5)
Oriental	3	(1.5)	0	(0.0)
Other	23	(11.4)	19	(9.1)
Total Number of Patients	202	(100.0)	209	(100.0)

Medical Reviewer's comments:
Patients were evenly distributed between the treatment groups based on age, weight, and race. There were slightly more males than females in both groups. The proportion of patients under 2 years of age in the Augmentin-90 and Augmentin-45 groups, respectively was 43.6% and 41.6%.

MO Table Demographic characteristics in study 25000/447 (based on FDA evaluable patients at F/U)

Demographic Characteristics	Augmentin-90 n	(%)	Augmentin-45 n	(%)
Age				
<6 mo	1	(0.9)	8	(6.7)
≥ 6 mo and < 2 yr	47	(40.5)	43	(35.8)
≥2 and < 5 yr	41	(35.3)	40	(33.3)
≥5 yr and < 8 yr	15	(13.9)	24	(20.0)
≥8 yr and < 12 yr	12	(10.3)	5	(4.2)
Mean [SD] (years)	3.29 [2.59]		3.2 [2.48]	
Minimum (years)	0.5		0.25	
Maximum (years)	10.2		11	
Weight (kg)				
<12 kg	39	(33.6)	55	(45.8)
≥ 12 kg and <23 kg	62	(53.4)	50	(41.7)
≥ 23 kg and <40 kg	15	(12.9)	15	(12.5)
Mean [SD]	15.38 [6.22]		14.86 [6.8]	
Minimum	7.0		6.0	
Maximum	40.0		39.7	
Gender				
Female	56	(48.3)	55	(45.8)
Male	60	(51.7)	65	(54.2)
Race				
White	82	(70.7)	96	(80.0)
Black	14	(12.1)	14	(11.7)
Oriental	3	(2.6)	0	(0)
Other	17	(14.7)	10	(8.3)
Total Number of Patients	116	(100.0)	120	(100.0)

Medical Reviewer's comments:
These results of demographic characteristics are similar to those in the previous table. I the FDA evaluable group summarized above, patients were evenly distributed between treatment arms, by weight, gender and race. Fewer patients under 6 months, and between 8 and 12 years, were randomized to the Augmentin-90 arm. The proportion of patients under 2 years of age in the FDA evaluable population was 41.4% and 42.5% in the Augmentin-90 and Augmentin-45 arms, respectively.

MO Table Diagnosis at Presentation (Baseline visit), Intent to Treat Population

Clinical Diagnosis	Augmentin-90 n (%)	Augmentin-45 n (%)
full bulging TM	149 (74.1)	152 (73.4)
absent or decreased mobility of TM	198 (98.5)	204 (98.6)
opacified TM	191 (95)	200 (96.9)

Medical Reviewer's comments:
Although 95% or more of the patients had otoscopic findings consistent with the presence of a middle ear effusion (i.e., decreased or absent mobility or opacification of the TM), the criterion most consistent with an acute process, fullness and bulging of the TM, was seen in approximately ¾ of the patients in each treatment arm.

MO Table Diagnosis at Presentation (Baseline visit), Evaluable Population

Clinical Diagnosis	Augmentin-90 n	Augmentin-45 n
Unilateral AOM	102	103
Right Ear	51	53
Left Ear	51	50
Bilateral AOM	49	48
Purulent/serous otorrhea		
Right ear	5	6
Left ear	7	5
Bilateral	0	1
Total patients	151	151

Medical Reviewer's comments:
This table includes patients who, although may have been excluded from the efficacy analysis, presented with a diagnosis of AOM. The numbers of patients with bilateral and unilateral AOM at baseline was essentially the same in the two treatment arms. Based on the reviewer's assessment, the remaining patients did not have AOM at presentation.
Although it was intention of the reviewer to include patients with history of repeated episodes of AOM (recurrent and chronic infections), the information, from center to center, was not consistently documented in the case report forms.

CLINICAL EFFICACY

SPONSOR'S RESULTS

Clinical Response At The End Of Therapy
Per Protocol Clinical Efficacy Population, All Patients Excluding Center 002

	Treatment Group			
	Augmentin-90		Augmentin-45	
	N	%	N	%
Clinical Response				
Success	137	82.5	146	86.9
Failure	29	17.5	22	13.1
Total Number Of Patients	166	100.0	168	100.0

95% CI [-12.1%, 3.3%]--Sponsor
95% CI [-12.7%, 3.9%]—FDA, with continuity correction

Sponsor's comment:
It was not expected that differences in efficacy could be detected in this study because the proportion of patients infected with *S. pneumoniae* with MICs >2.0 is relatively small.

Medical reviewer's comments:
Because there were no microbiologic investigations performed in this study, it is impossible to say how many, if any, of the patients had drug resistant *S. pneumoniae* as the pathogen associated with their AOM .

Clinical Outcome At Follow-Up
Per Protocol Clinical Efficacy Population, All Patients Excluding Center 002

	Treatment Group			
	Augmentin-90		Augmentin-45	
	N	%	N	%
Clinical Outcome				
Persistent Clinical Cure	111	84.1	108	78.8
Clinical Recurrence	21	15.9	29	21.2
Total Number Of Patients	132	100.0	137	100.0

Medical reviewer's comments:
Since the sponsor used the end of therapy visit for the assessment of final outcome, failures at the end of therapy visit were not carried forward to the end of study (follow-up) assessment. The clinical outcome reported in the table above is therefore based on patients who were successes at the end of therapy. However, using the sponsor's data, failures were carried forward by the reviewer and are included in the assessment of the clinical response at the end of study, summarized in the next table.

MO Table Clinical response at the End of the Study (follow-up), Sponsor's per-protocol clinical efficacy population
All patients excluding Center 002

	Augmentin 90 N	%	Augmentin 45 N	%
Clinical Response				
Cure	111	68.9	108	67.9
Recurrence	21	13.0	29	18.2
Failure (from day EOT)	29	18.0	22	13.8
Total	161		159	

95% CI [-9.2%, 11.2%]—Sponsor
95% CI [-9.8%, 11.8%]—FDA, with continuity correction

Medical officer's comments:
As expected, the cure rates were lower than those seen at the end of therapy. The rates are similar between the two treatment arms.

MEDICAL REVIEWER'S RESULTS

Table Clinical response at the follow-up using FDA evaluable patients (per protocol, excluding site 002)

	Per Protocol			
Clinical Response	Augmentin-90 n	(%)	Augmentin-45 n	(%)
Success	96	(82.8)	94	(78.3)
Failure	20	(17.2)	26	(21.7)
Total No. of Patients	116	(100.0)	120	(100.0)

Treatment Difference 4.4%
95% CI (-6.5%, 15.4%)

Medical reviewer's comments:
The efficacy rates at the follow-up visit for the FDA evaluable population were slightly lower in the Augmentin-45 group, but the difference was not statistically significant. The lower bound of 95% confidence interval for the difference in response rates (Augmentin-90 vs. Augmentin-45) is above the Points-To-Consider document recommended cut-off for equivalence of -15%. There were 13 patients who received antimicrobial agents within 7 days of study initiation, 6 in the Augmentin-90 arm and 7 in the Augmentin-45 arm. The presence of drug-resistant *S. pneumoniae* would be more likely in these patients with prior antimicrobial exposure. In these 13 patients, 3/6 in the Augmentin-90 arm were clinically cured while 4/7 in the Augmentin-45 arm were successes. Because the numbers are small, no generalizations can be made about the difference in efficacy for Augmentin-90 vs. Augmentin-45 in the treatment of these patients.

MO Table Clinical response by demographic characteristics in study 25000/447 FDA evaluable population at follow-up (excluding site 002)

	Augmentin-90 n	(%)	Augmentin-45 n	(%)
Age				
< 6 months				
Success	1	(100.0)	6	(75.0)
Failure	0	(0.0)	2	(25.0)
> 6 mos to < 2 yr				
Success	38	(80.9)	29	(67.4)
Failure	9	(19.1)	14	(32.6)
≥ 2 yr to < 5 yr				
Success	34	(82.9)	32	(80.0)
Failure	7	(17.1)	8	(20.0)
≥ 5 yr to < 8 yr				
Success	14	(93.3)	22	(91.7)
Failure	1	(6.7)	2	(8.3)
≥ 8 yr to < 12 yr				
Success	9	(75.0)	5	(100.0)
Failure	3	(25.0)	0	(0.0)
Gender				
Female				
Success	45	(80.4)	41	(74.5)
Failure	11	(19.6)	14	(23.5)
Male				
Success	51	(85.0)	53	(81.5)
Failure	9	(15.0)	12	(19.5)
Race				
Black				
Success	12	(85.7)	10	(71.4)
Failure	2	(14.3)	4	(28.6)
White				
Success	65	(79.3)	77	(80.2)
Failure	17	(21.7)	19	(19.8)
Oriental				
Success	3	(100)	0	
Failure	0		0	
Other*				
Success	16	(94.1)	7	(70.0)
Failure	1	(5.9)	3	(30.0)
Total No. of Patients	116		120	

* Other: Hispanic, Asian, Asian Indian, Biracial (white/Asian), Biracial (white/black), Filipino, Indian, Pakistani, Samoan.

Medical reviewer's comments:
Some differences were noted in the success rates due to age. Success rates were higher in the Augmentin-90 arm for children under 2 years of age and higher in the Augmetin-45 arm for children over 8 years of age . Response rates based on the other demographic variables were comparable between treatment arms. Because the history of recurrent and chronic OM infections was inconsistently documented among the sites, it was not possible to do a secondary efficacy analysis using these parameters.

Without correlative bacteriologic data from tympanocentesis, it is difficult to attribute failures to a specific pathogen, and in particular to *S. pneumoniae*. Additionally, since delayed resolution of symptoms and failure can be associated with the presence of a concomitant viral infection in the middle ear, which occurs in 40-45% of cases of AOM, the true drug effects must be considered in this context. Spontaneous resolution rates of acute otitis media (20% for *Pneumococcus*, 50% for *H. influenzae* and 70% for *Moraxella catarrhalis*), the lack of knowledge of the pathogen distribution in each treatment arm, and the possibility of culture-negative AOM must also be considered when interpreting these data.
Therefore, conclusions about the potential effectiveness of the high dose Augmentin regimen against *S. pneumoniae*, including drug-resistant *S. pneumoniae*, based on these clinical efficacy data may not be reliable.

SAFETY

Deaths and Serious Non-Fatal Adverse Experiences

There were no deaths reported during the study period. One serious adverse event (SAE) of accidental overdose was reported for a patient in the Augmentin-90 group.
Patient 11-227: A 3.5 year old male Caucasian patient with AOM inadvertently received two overdoses of study medication. The patient received Augmentin 90/6.4 mg/kg/day q12h based on a recorded weight of 18 kg; the weight was later corrected to 13.4 kg. Approximately 1 hour after the overdose, he experienced mild emesis. No further episodes of emesis occurred after the patient received the second overdose. The patient continued in the study, and the dose was adjusted to his correct weight. He experienced no further sequelae and completed the study. The investigator, who remained blinded to treatment assignment, considered both the overdose (SAE) and the emesis to be unrelated to the study medication.

Medical reviewer's comments:
It is not clear to the reviewer why the adverse events in this patient are considered as unrelated to the study drug.

Adverse events and Withdrawals

A total of 199/408 patients (48.8%) in the ITT population reported AEs (on-therapy to 30 days post-therapy). Of the 199 patients (excludes patients from site 002), 13 had at least one AE that led to withdrawal. The AE responsible for the highest rate of withdrawals was vomiting in both treatment groups. Three patients withdrew from the study due to diarrhea. Patients who withdrew due to diarrhea were considered to have fulfilled the criteria for LDD. Two patients in the Augmentin-90 group withdrew, one on Day 1 and one on Day 3. In the Augmentin-45 group the sole withdrawal due to diarrhea occurred on Day 5.

Incidence Of Adverse Experiences Leading To Withdrawal By Body System And Preferred Term
Intent-To-Treat Population, Phase = On-Therapy To 30 Days Post-Therapy

	N	WHO BODY SYSTEM	PREFERRED TERM	PID
AUGMENTIN-90				
	1	GASTROINTESTINAL SYSTEM	ABDOMINAL PAIN	447.004.00133
	2	GASTROINTESTINAL SYSTEM	DIARRHEA	447.003.00002 447.016.00187
	3	GASTROINTESTINAL SYSTEM	VOMITING	447.011.00221 447.015.00334 447.018.00441
	1	SKIN AND APPENDAGES	ERYTHEMA MULTIFORME	447.015.00324
	1	SKIN AND APPENDAGES	PRURITUS GENITAL	447.004.00133
	1	SKIN AND APPENDAGES	URTICARIA	447.014.00352
	1	WHITE CELL AND RETICULOENDOTHELIAL SYSTEM	LYMPHADENOPATHY	447.001.00584
	1	WHITE CELL AND RETICULOENDOTHELIAL SYSTEM	LYMPHADENOPATHY CERVICAL	447.001.00584
AUGMENTIN-45				
	1	GASTROINTESTINAL SYSTEM	DIARRHEA	447.001.00599
	1	GASTROINTESTINAL SYSTEM	GASTROENTERITIS	447.016.00182
	2	GASTROINTESTINAL SYSTEM	VOMITING	447.012.00286 447.015.00332

Medical reviewer's comments:
Gastrointestinal complaints were the main reason for withdrawals. Six patients were withdrawn from the Augmentin-90 arm for GI problems compared with 4 withdrawals for GI complaints from the Augmentin-45 group.

Number (%) Of Patients Reporting Adverse Experiences By Body System ITT Population, All Patients Excluding Center 002
Phase = On-Therapy To 30 Days Post-Therapy

TREATMENT	AUGMENTIN-90		AUGMENTIN-45		TOTAL	
TOTAL NUMBER OF PATIENTS :	201	100.0%	207	100.0%	408	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	101	50.2%	98	47.3%	199	48.8%
WHO BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
APPLICATION SITE	12	6.0	10	4.8	22	5.4
DERMATITIS CONTACT	12	6.0	10	4.8	22	5.4
BODY AS A WHOLE GENERAL	18	9.0	13	6.3	31	7.6
FATIGUE	1	0.5	0	0.0	1	0.2
FEVER	11	5.5	8	3.9	19	4.7
INJURY	3	1.5	2	1.0	5	1.2
MALAISE	2	1.0	2	1.0	4	1.0
PAIN	1	0.5	1	0.5	2	0.5
THERAPEUTIC RESPONSE INCREASED	1	0.5	0	0.0	1	0.2
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	5	2.5	1	0.5	6	1.5
DYSPHONIA	1	0.5	0	0.0	1	0.2
HEADACHE	3	1.5	0	0.0	3	0.7
HYPERKINESIA	1	0.5	0	0.0	1	0.2
TREMOR	0	0.0	1	0.5	1	0.2
GASTROINTESTINAL SYSTEM	31	15.4	25	12.1	56	13.7
ABDOMINAL PAIN	8	4.0	4	1.9	12	2.9
ANOREXIA	1	0.5	0	0.0	1	0.2
CONSTIPATION	1	0.5	1	0.5	2	0.5
DIARRHEA	3	1.5	2	1.0	5	1.2
DYSPEPSIA	2	1.0	1	0.5	3	0.7
FLATULENCE	0	0.0	1	0.5	1	0.2
GASTROENTERITIS	1	0.5	2	1.0	3	0.7
NAUSEA	2	1.0	0	0.0	2	0.5
TOOTH ACHE	6	3.0	1	0.5	7	1.7
VOMITING	13	6.5	16	7.7	29	7.1
HEARING AND VESTIBULAR	2	1.0	2	1.0	4	1.0
EAR DISORDER NOS	1	0.5	0	0.0	1	0.2
EARACHE	1	0.5	2	1.0	3	0.7
PLATELET BLEEDING AND CLOTTING	1	0.5	0	0.0	1	0.2
PURPURA	1	0.5	0	0.0	1	0.2
PSYCHIATRIC	2	1.0	0	0.0	2	0.5

SOMNOLENCE	2	1.0	0	0.0	2	0.5
REPRODUCTIVE MALE						
PENIS DISORDER	2	1.0	0	0.0	2	0.5
	2	1.0	0	0.0	2	0.5
RESISTANCE MECHANISM						
HERPES SIMPLEX	24	11.9	30	14.5	54	13.2
HERPES ZOSTER	0	0.0	1	0.5	1	0.2
INFECTION	0	0.0	1	0.5	1	0.2
INFECTION BACTERIAL	1	0.5	1	0.5	2	0.5
INFECTION FUNGAL	0	0.0	2	1.0	2	0.5
INFECTION VIRAL	7	3.5	4	1.9	11	2.7
MONILIASIS	7	3.5	2	1.0	9	2.2
MONILIASIS GENITAL	4	2.0	3	1.4	7	1.7
OTITIS MEDIA	0	0.0	1	0.5	1	0.2
UPPER RESP TRACT INFECTION	1	0.5	0	0.0	1	0.2
	6	3.0	19	9.2	25	6.1
RESPIRATORY SYSTEM						
ASTHMA	37	18.4	34	16.4	71	17.4
BRONCHITIS	1	0.5	2	1.0	3	0.7
BRONCHOSPASM	1	0.5	1	0.5	2	0.5
COUGHING	0	0.0	2	1.0	2	0.5
PHARYNGITIS	24	11.9	14	6.8	38	9.3
PNEUMONIA	6	3.0	3	1.4	9	2.2
RHINITIS	1	0.5	1	0.5	2	0.5
SINUSITIS	8	4.0	9	4.3	17	4.2
SPUTUM INCREASED	0	0.0	4	1.9	4	1.0
STRIDOR	0	0.0	1	0.5	1	0.2
	2	1.0	1	0.5	3	0.7
SKIN AND APPENDAGES						
DERMATITIS FUNGAL	16	8.0	11	5.3	27	6.6
ERYTHEMA MULTIFORME	1	0.5	1	0.5	2	0.5
PRURITUS GENITAL	1	0.5	2	1.0	3	0.7
RASH	2	1.0	0	0.0	2	0.5
RASH ERYTHEMATOUS	7	3.5	6	2.9	13	3.2
RASH MACULO-PAPULAR	2	1.0	0	0.0	2	0.5
URTICARIA	1	0.5	0	0.0	1	0.2
	2	1.0	2	1.0	4	1.0
URINARY SYSTEM						
MICTURITION FREQUENCY	2	1.0	0	0.0	2	0.5
OLIGURIA	1	0.5	0	0.0	1	0.2
	1	0.5	0	0.0	1	0.2
VASCULAR EXTRACARDIAC						
CRAMPS LEGS	0	0.0	1	0.5	1	0.2
	0	0.0	1	0.5	1	0.2
VISION						
CONJUNCTIVITIS	3	1.5	3	1.4	6	1.5
	3	1.5	3	1.4	6	1.5
WHITE CELL AND RETICULOENDOTHELIAL SYSTEM						
LYMPHADENOPATHY	1	0.5	0	0.0	1	0.2
	1	0.5	0	0.0	1	0.2

LYMPHADENOPATHY CERVICAL	1	0.5	0	0.0	1	0.2

Medical reviewer's comments:
In general, the most common adverse effects associated with the administration of amoxicillin-clavulanate are gastrointestinal in nature and include diarrhea, nausea and vomiting, with incidences of approximately 4.1%, 3%, and 1.8%, respectively (Reed M. Clinical Pharmacokinetics of amoxicillin and clavulanate. Ped Inf Dis J. 1996;14:949-54). From this table, the reports of diarrhea and nausea were lower than what would be expected, while the rate of vomiting was about 3 times higher. However, after reviewing the CRFs, the reviewer considers 3 patients presented in this table with gastroenteritis (1 in the Augmentin-90 and 2 in the Augmentin-45 arm) to have had diarrhea. The first patient had rotaviral infection and the second diarrhea and gastroenteritis. The only description provided on the CRF for the third patient is gastroenteritis.

Number (%) Of Patients Reporting Adverse Experiences By Preferred Term Ordered By Decreasing Frequency
Intent-To-Treat Population, Excluding Center 002 Phase = On-Therapy To 30 Days Post-Therapy

TREATMENT	AUGMENTIN-90		AUGMENTIN-45		TOTAL	
TOTAL NUMBER OF PATIENTS :	201	100.0%	207	100.0%	408	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	101	50.2%	98	47.3%	199	48.8%
PREFERRED TERM	N	%	N	%	N	%
COUGHING	24	11.9	14	6.8	38	9.3
VOMITING	13	6.5	16	7.7	29	7.1
DERMATITIS CONTACT	12	6.0	10	4.8	22	5.4
FEVER	11	5.5	8	3.9	19	4.7
RHINITIS	8	4.0	9	4.3	17	4.2
ABDOMINAL PAIN	8	4.0	4	1.9	12	2.9
RASH	7	3.5	6	2.9	13	3.2
INFECTION FUNGAL	7	3.5	4	1.9	11	2.7
INFECTION VIRAL	7	3.5	2	1.0	9	2.2
UPPER RESP TRACT INFECTION	6	3.0	19	9.2	25	6.1
PHARYNGITIS	6	3.0	3	1.4	9	2.2
TOOTH ACHE	6	3.0	1	0.5	7	1.7
MONILIASIS	4	2.0	3	1.4	7	1.7
CONJUNCTIVITIS	3	1.5	3	1.4	6	1.5
DIARRHEA	3	1.5	2	1.0	5	1.2
INJURY	3	1.5	2	1.0	5	1.2
HEADACHE	3	1.5	0	0.0	3	0.7
MALAISE	2	1.0	2	1.0	4	1.0
URTICARIA	2	1.0	2	1.0	4	1.0

DYSPEPSIA	2	1.0	1	0.5	3	0.7
STRIDOR	2	1.0	1	0.5	3	0.7
NAUSEA	2	1.0	0	0.0	2	0.5
PENIS DISORDER	2	1.0	0	0.0	2	0.5
PRURITUS GENITAL	2	1.0	0	0.0	2	0.5
RASH ERYTHEMATOUS	2	1.0	0	0.0	2	0.5
SOMNOLENCE	2	1.0	0	0.0	2	0.5
ASTHMA	1	0.5	2	1.0	3	0.7
EARACHE	1	0.5	2	1.0	3	0.7
ERYTHEMA MULTIFORME	1	0.5	2	1.0	3	0.7
GASTROENTERITIS	1	0.5	2	1.0	3	0.7
BRONCHITIS	1	0.5	1	0.5	2	0.5
CONSTIPATION	1	0.5	1	0.5	2	0.5
DERMATITIS FUNGAL	1	0.5	1	0.5	2	0.5
INFECTION	1	0.5	1	0.5	2	0.5
PAIN	1	0.5	1	0.5	2	0.5
PNEUMONIA	1	0.5	1	0.5	2	0.5
ANOREXIA	1	0.5	0	0.0	1	0.2
DYSPHONIA	1	0.5	0	0.0	1	0.2
EAR DISORDER NOS	1	0.5	0	0.0	1	0.2
FATIGUE	1	0.5	0	0.0	1	0.2
HYPERKINESIA	1	0.5	0	0.0	1	0.2
LYMPHADENOPATHY	1	0.5	0	0.0	1	0.2
LYMPHADENOPATHY CERVICAL	1	0.5	0	0.0	1	0.2
MICTURITION FREQUENCY	1	0.5	0	0.0	1	0.2
OLIGURIA	1	0.5	0	0.0	1	0.2
OTITIS MEDIA	1	0.5	0	0.0	1	0.2
PURPURA	1	0.5	0	0.0	1	0.2
RASH MACULO-PAPULAR	1	0.5	0	0.0	1	0.2
THERAPEUTIC RESPONSE INCREASED	1	0.5	0	0.0	1	0.2
SINUSITIS	0	0.0	4	1.9	4	1.0
BRONCHOSPASM	0	0.0	2	1.0	2	0.5
INFECTION BACTERIAL	0	0.0	2	1.0	2	0.5
CRAMPS LEGS	0	0.0	1	0.5	1	0.2
FLATULENCE	0	0.0	1	0.5	1	0.2
HERPES SIMPLEX	0	0.0	1	0.5	1	0.2
HERPES ZOSTER	0	0.0	1	0.5	1	0.2
MONILIASIS GENITAL	0	0.0	1	0.5	1	0.2
SPUTUM INCREASED	0	0.0	1	0.5	1	0.2
TREMOR	0	0.0	1	0.5	1	0.2

No data were available on adverse experiences after 30 days post-therapy.

Medical reviewer's comments:

In addition to the adverse events discussed in the comment above, abdominal pain was noted twice as often among patients in the Augmentin-90 arm. Overall, there were no significant differences noted in the adverse events between the two groups.

Number (%) Of Patients With Protocol Defined Diarrhea (PDD)
Intent-To-Treat Bowel Habit Population, excluding site 002

	Treatment Group			
	Augmentin-90		Augmentin-45	
	N	%	N	%
PDD				
No	179	89.1	189	91.3
Yes	22	10.9	18	8.7
Total Number Of Patients	201	100.0	207	100.0

Reviewer's comments:
After a blind review of the patient diaries for documentation of patient stooling patterns, the reviewer agreed with the applicant's assessment regarding patients with PDD in the intent-to-treat group, with the exception of 1 patient. Patient 012-292 in the Augmentin-45 arm who did not have protocol defined diarrhea, but was included by the sponsor. The table reflects the exclusion of this patient. From these results, there is no significant treatment difference in the rate of protocol defined diarrhea.

CONCLUSIONS

1) A single study, without bacteriologic data, is not sufficient to support the claim of efficacy for acute otitis media due to drug-resistant S. *pneumoniae*. The proportion, if any, of clinical failures due to drug-resistant *S. pneumoniae,* and the interpretation of the efficacy data in the face of high overall rates of spontaneous resolution and concurrent viral AOM, cannot be determined without supporting microbiologic data.

2) Clinical data to support T>MIC as surrogate endpoint for clinical efficacy are limited; at the present time, PK/PD parameters including T>MIC, best serve as adjuncts to support the design of clinical trials. Therefore, data on T>MIC as an alternative to the demonstration of efficacy in clinical trials are not sufficient for the approval of antimicrobial agents.

3) The role of clavulanate against *S. pneumoniae* as supported by microbiologic data, is not clearly defined. The need for the combination product, Augmentin rather than amoxicillin alone for the treatment of drug-resistant *S. pneumoniae* has not been supported in the application. Thus, there is no basis for the inclusion of *S. pneumoniae* as a pathogen in the second list of the Microbiology section of the label.

4) With the availability of lower doses of Augmentin, no data has been provided to support the use of higher doses of Augmentin to treat patients with AOM due to *H. influenzae* and *Moraxella catarrhalis*.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS

NDA 50-755, Augmentin DS for acute otitis media due to drug-resistant *S. pneumoniae* is not recommended for approval. Bacteriologic data are necessary to demonstrate the efficacy of Augmentin 14:1 formulation against (drug-resistant) *S. pneumoniae* causing acute otitis media.

/S/

Mamodikoe Makhene, M.D.
Medical Officer/HFD-520

cc:
original IND, NDA
NDA 50-755
HFD-520/ Div Director/Chikami /S/ 10/26/98
HFD-520/ Deputy Div Director/Gavrilovich
HFD-520/Medical TL/Albuerne /S/ 9/3/98
HFD-344/DSI/Thomas
HFD-520/PharmTox/Seethaler
HFD-520/Chemistry/Yu
HFD-520/Microbiology/Altaie
HFD-520/Biopharm/Sun
HFD-520/CSO/Trostle
mkm/8/07/98

LITERATURE REVIEW

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