CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-755

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW
NDA 50-755, AUGMENTIN ES (90 mg/kg/day ORAL SUSPENSION--14:1 formulation) for Acute Otitis Media due to penicillin resistant *S. pneumoniae*

Applicant identification: SmithKline Beecham Pharmaceuticals (SB)
Philadelphia, PA 19101
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215-751-3468

Submission/Review Dates
Date of submission: April 5, 2000
Date received: April 14, 2000
Date review begun: May 16, 2000
Date draft completed: September 28, 2000
Review completed: October 3, 2000

DRUG IDENTIFICATION

Generic Name:	amoxicillin-clavulanate potassium
Proposed Trade Name:	Augmentin ES
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
Dosage Form:	suspension
Route of Administration:	oral

Related Drugs
Amoxicillin is available as 40mg/kg/day and 45mg/kg/day (in generic form) all over the world. Amoxicillin-clavulanic acid is available today in the United States as 40mg/kg/day and 45mg/kg/ and in Europe as co-amoxyclav.

I. INTRODUCTION AND BACKGROUND

A. Proposed Indication (taken from proposed label)

INDICATIONS AND USAGE
Augmentin ES is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:
Acute Otitis Media—caused by β-lactamase-producing strains of *H. influenzae or M. catarrhalis*, and *S. pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥2 μg/mL) when suspected.
Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin ES*, should be performed if indicated. Infections caused by *S. pneumoniae*, including penicillin-resistant strains, are amenable to treatment with *Augmentin ES* due to its amoxicillin content.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin ES* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

DOSAGE AND ADMINISTRATION (taken from the proposed label)
Dosage:
Pediatric patients aged 12 weeks (3 months) and older
The recommended dose of *Augmentin ES* is 90 mg/kg/day divided q12h, based on the amoxicillin component.

B. Important milestones in Product Development/Regulatory Background
August 21, 1995 (From SB minutes of teleconference)
"FDA attendees expressed concern about the regulatory dilemma of approval based on clinical safety data and time above minimum inhibitory concentration (T>MIC) arguments, in the absence of correlation between clinical outcome and microbiology. The sponsor argued that the low prevalence of resistant *S. pneumoniae* made conducting a study difficult."

October 21, 1996
The medical officer's review of protocol 25000/447, a study in patients with acute otitis media without collection of bacteriologic data, raised concern about the lack of a microbiologic component to the efficacy analysis which would lead to an inability to draw any conclusion about the effectiveness of the antibiotic agent against penicillin resistant *S. pneumoniae*.

January 23, 1997
(from SB meeting minutes)
Face-to-face meeting between FDA and SB to discuss whether a clinical safety study, and clinical pharmacokinetic (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 NDA for the Augmentin 14:1 formulation; the Division agreed that SB proposal was reviewable.

October 31, 1997
Original NDA 50-755, Augmentin 90mg/kg/day ("Augmentin DS", the original proposed name for this formulation) for acute otitis media due to drug resistant *S. pneumoniae*; was submitted.

December 16, 1997
Face to face meeting held with SB to discuss the lack of a microbiology study and the use instead of a pharmacokinetic/pharmacodynamic (PK/PD) surrogate (T>MIC) to support efficacy claim of Augmentin DS for the empiric treatment of drug-resistant *S. pneumoniae*.

October 16, 17, 1998
Consensus reached during Anti-Infectives Advisory Committee meeting that non-clinical data could act as correlates, but not surrogates, for clinical data.

October 31, 1998
NDA 50-755 not approved for lack of bacteriologic data to support efficacy claim. In addition, the nomenclature did not approve the use of the name Augmentin DS.

February 25, 1999
Telecon with SB to discuss reviewer's comments on protocol, submitted in January, for bacteriologic study; reviewer's comments sent by facsimile to sponsor

April 5, 2000
Resubmission of NDA for new formulation, now called Augmentin ES, with response to non-approval letter of October, 1998

May 24/25, 2000
Medical officer request to SB (Cindy D'Ambrosio, Regulatory Affairs) for:
- The CRFs not provided in the submission
- Location of the line listings (SB response: available in SAS for the reviewer to create)
- Efficacy data by site
- Safety update and information regarding informed consent in foreign sites.

June 7, 2000
Electronic CRFs for all patients received.
Medical reviewer and FDA statistician, Erica Brittain, met with SB representatives (Dr. D'Ambrosio and 2 statisticians) to discuss FDA request for a master variables listing for patients in study 536.

June 22, 2000
Telecon between SB representative, Cindy D' Ambrosio and FDA (Project Manager, Dr. Samanta and medical reviewer) to discuss the following:
- the electronic CRFs (eCRFs) appear to be an abbreviated form of the workbook.
- interim visit documentation and bacteriologic culture results not found in eCRFs
- responses to queries provided with eCRFs unclear at times
- request for hard copy records (CRFs) for all patients.

June 27, 2000
Mathew Thomas, MD, Division of Scientific Investigations (DSI) of CDER contacted by reviewer to request inspection of site 600 in Israel.
Teleconference between SB (Cindy D'Ambrosio, Deneen Stewart) and FDA (Susmita Samanta, Erica Brittain, medical reviewer):
FDA informed by SB that culture report form was not considered part of the workbook/ CRF--data were kept at the sites and are also available in the submitted datasets.

July 6, 2000

Desk copy of super536 data set (master variables patient listing) received.

July 11, 2000
SB (Cindy D' Ambrosio) informed reviewer that paper CRFs do not exist; remote data management system was primary method to capture data. SB refused to provide workbooks (CRFs) because workbooks were inconsistently completed by the investigators and have never been examined by SB; SB willing to provide revised electronic CRFs.

July 13, 2000
Written comments about the availability of paper CRFs received from SB (discussed with Dr. El Hage, DSI).

August 3, 2000
Revised electronic CRFs for patients with *S. pneumoniae* isolates received.

August 17, 21, 31, 2000
Review questions sent to SB, including queries about the evaluability of patients who failed treatment for AOM but were non-evaluable in the applicant's efficacy analysis.

August 31, 2000
Microbiologic lab results from the reference lab received.

September 6, 2000
Telecon with SB (D' Ambrosio) to discuss large number of documented clinical failures who received concomitant antibiotics but are not evaluable in the applicant's efficacy analysis.

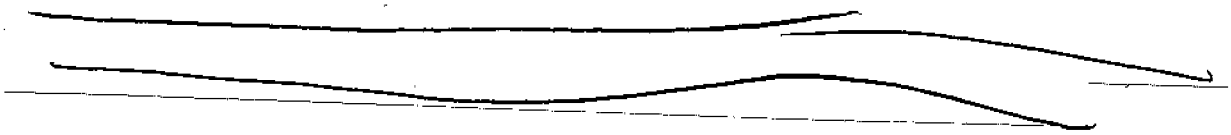
September 13, 2000
Telecon between SB (C. D'Ambrosio) and FDA attendees (S Samanta, G Chikami, M Makhene, M Albuerne, E Brittain) to discuss the large numbers of clinical failures considered non-evaluable; SB confirmed that a programming error (suspected before FDA queries) had occurred; data reanalysis underway.

September 14, 2000
FDA (M Makhene, F Lesane) request for clarification of the nature of programming error and expected impact on NDA

September 21/22, 2000
Revised data analysis (e-mail), revised datasets and master variables patient listing received.

September 27, 2000
Revised safety update report received.

C. **Other relevant information/Marketing history in other countries**
NDA 50-755 was originally submitted in October 1997; the claim of efficacy was supported by a single clinical study (without bacteriologic data) and a pharmacokinetic study intended to demonstrate adequate T>MIC for Augmentin 90mg/kg/day. The application was not approved for lack of bacteriologic data to demonstrate efficacy in patients with drug (penicillin) resistant *S. pneumoniae,* and T>MIC was not accepted as a surrogate for bacteriologic efficacy.
Clinical trials have been conducted, using higher doses of Augmentin---60/15mg/kg/day and 70/10 mg/kg/day, in 5 countries. SB reports that no safety problems were encountered in these studies. Approval for amoxicillin/clavulanic acid 80mg/kg/day for infants 1-30 months of age was granted in France in 1992.



II. Relevant findings from other disciplines
Chemistry
See review by A. Yu, Ph.D.
SB reports stability issues with raspberry orange flavoured syrup; results to date indicate that there are good stability data for up to 9 months.

Animal Pharmacology/Toxicology
See review by K. Seethaler, Ph.D.
Pharmacology/toxicology reviewer does not object to approval of the NDA. There are no pre-safety concerns with Augmentin, and the label is considered to be acceptable as written.

Microbiology
See review by S. Altaie, Ph.D.
Because of the lack of bacteriologic efficacy data for patients with *S. pneumoniae* alone in the middle ear, a determination of the interpretive criteria for *in vitro* susceptibility testing is not possible.

III. **Human PK/PD**
No new data submitted.
See original review of pharmacokinetic study 447 by H. Sun, Ph.D.

REGULATORY GUIDANCE DOCUMENTS
The Points to Consider Document of the Division of Anti-infective Drug Products
Two clinical trials are suggested for acute otitis media:

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

post-therapy tympanocentesis of failures to determine persistence or superinfection

The IDSA/FDA guidelines

- The control drug should have proven activity against *Haemophilus influenzae, Moraxella catarrhalis* and *S. pneumoniae*.
- All children who receive systemic antibacterial agents within the 7 days before study entry should be excluded.
- Consider second aspirates from those who fail therapy clinically at least 72 hours after study drug initiation.
- Expect effective agent to sterilize MEF in >80% of patients within 72 hours
- 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.
- Each diseased ear should be aspirated for bacteriologic assessment.

Divisional Evaluability Criteria–Evaluating Clinical Studies of Antimicrobials

The clinical diagnosis of OM must be based on:

1. history and physical examination
2. 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, and
3. 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)-samples from perforated TMs are acceptable if perforation is <48 hours old
- 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 considered a failure. Tympanocentesis is recommended for patients judged to be failing therapy.

Advisory Committee Recommendations (March 1997)-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 at the time of failure

Advisory Committee Recommendations (July 1998)-AOM Guidance Document

- Drugs to be approved must show activity against the three major AOM pathogens
- Documentation of bulging TM at study entry is important
- Biphasic pneumatic otoscopy recommended to document AOM; electroacoustic reflectometry or tympanometry would be useful to demonstrate the presence of an effusion
- TOC visit 2-4 weeks after entry into study
- Drug Resistant *S. pneumoniae* (DRSP) Working Group recommends that repeat tympanocentesis day 3-5 of study is critical measure of treatment efficacy and for approval; repeat tympanocentesis at day 3-5 can be limited to treatment failures, and patients with resistant organism (e.g., non-susceptible pneumococci) at baseline
- Inclusion of patients with acutely perforated TM acceptable [for *Streptococcus pneumoniae* or group A streptococcus (*Streptococcus pyogenes*) only (Reller) or for all AOM pathogens (Craig)]
- To better detect differences in clinical response, tighten inclusion criteria in clinical only study, and enrich the population with patients under 2 years of age
- No consensus on the number of *Streptococcus pneumoniae* isolates needed

IV. **Review Methods**

The NDA was provided for review as an electronic submission. Comments on the original protocol and all communications between the FDA and applicant pertaining to this application were reviewed. In addition, the proposed label, protocol, study report, and electronic case report forms (eCRFs) were reviewed. Because of the rationale for the development of this drug, the review concentrated on patients with penicillin resistant *Streptococcus pneumoniae*. Information concerning patients with penicillin susceptible *Streptococcus pneumoniae* and other pathogens (small random sample), and non-evaluable patients in the applicant's analysis (protocol violators, those who received concomitant antibiotics, and withdrawals) was also examined. Bacteriologic results from the reference lab and a master variables listing for all patients were also reviewed.

Data quality and integrity

Inspections were requested for sites with the largest enrollment—Pittsburgh, Israel, Costa Rica and Guatemala. DSI agreed to inspect 2 US (Pittsburgh, Scottsdale) and 2 non-US sites (Costa Rica, Guatemala); since the Israeli site had been inspected within the year, and no problems were noted at that time, DSI was of the opinion that a reinspection was not necessary.

However, initial review of some of the CRFs from the Israeli site revealed some inconsistencies, and a site inspection was requested again. The reviewer was advised by DSI to seek clarification of the inconsistencies by comparing the paper CRFs with the eCRFs. However, the paper CRFs were not available to the reviewer (eCRFs considered the official source documents by the sponsor and the paper CRFs were not consistently completed at the sites). DSI then recommended a review of the electronic audit trails for *S. pneumoniae* patients at this site. Review of this information revealed no unusual activities. In addition, the DSI inspections of the 4 sites mentioned above revealed no significant deficiencies, and DSI had concluded that the data from the inspected sites appear acceptable.

V. **Data sources**

A. Data were derived from a clinical/microbiologic study conducted at multiple sites.
B. No postmarketing experience exists since the formulation is not yet approved.

Ethics (taken from study report)

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki as amended in the Republic of South Africa, October 1996 by the 48th General Assembly. In addition, this study was conducted according to the Code of Federal Regulations (CFR) and relevant FDA regulations and SB's Good Clinical Practice (GCP) Standard Operating Procedures. The protocol and statement of informed consent were approved by an Institutional Review Board (or Ethics Committee) prior to each center's initiation. Written informed consent was obtained from each patient's parent/legal guardian prior to entry into the study. Remote Data Management and Patient Workbooks were provided for the documentation of each patient's data.

VI. **Efficacy Review**

CLINICAL STUDIES

STUDY DESIGN SUMMARY

Study 25000/536

Primary Objective	To obtain bacteriological efficacy data for *Augmentin* ES in the treatment of children with AOM due to *S. pneumoniae* with penicillin MICs of ≥ 2.0 mcg/mL To obtain bacteriological efficacy data for *Augmentin* ES in the treatment of children with AOM due to *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4.0 mcg/mL.
Secondary Objective	Demonstration of the clinical efficacy of *Augmentin* ES in patients infected with *S. pneumoniae* including isolates with amoxicillin/clavulanic acid MICs of 4.0 mcg/mL and in patients infected with *S. pneumoniae* including isolates with penicillin MICs of ≥ 2.0 mcg/mL. Assessment of the clinical and bacteriological efficacy of *Augmentin* ES in patients with AOM due to any pathogen.
Study design	Open label, non-comparative, multi-center study
Study dates	24 February, 1999 to November 5, 1999
Patients Population	males and females; 3 months to 48 months
Location	US-21 sites; Foreign-4 sites
Study drug dosing/duration	*Augmentin* 90/6.4 mg/kg/day every 12 hours for 10 days
Inclusion Criteria	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.
Exclusion Criteria	spontaneous perforation of the tympanic membrane and drainage for longer than 24 hours; tympanoplastic tube(s) in place, or anatomic abnormalities associated with prolonged middle ear effusion
Evaluation visits	Baseline On therapy visit days 4-6 Interim visit as needed End of therapy days 12-15 Test of Cure days 25-28
Procedures	• Tympanocentesis at the preliminary visit or if the membrane is ruptured with purulent effusion of less than 24 hours duration, direct culture may be obtained • second tympanocentesis: All patients with *S. pneumoniae* (alone or with other pathogens): at day 4-6 preliminary visit. All other patients: **A:** for treatment failure only OR **B:** all patients at day 4-6.
SB 1° Efficacy Parameter	bacteriological response of *Streptococcus pneumoniae* in the per protocol bacteriological population on day 4-6.
FDA 1° Efficacy parameter	Bacteriologic outcome based on clinical response at TOC
Secondary efficacy parameters	1) bacteriological response of other pathogens to study medication at the on-therapy visit (day 4-6), and presumed bacteriological response of other pathogens to study medication at the test of cure visit (day 25-28), 2) clinical response (clinical cure or clinical failure) at the end-of-treatment visit (day 12-15), and 3) clinical response (clinical cure, clinical failure, or clinical recurrence) at the test-of-cure visit (day 25-28).

Rationale (from original submission)

SmithKline Beecham recognizes that *Streptococcus pneumoniae* is a non-β-lactamase producing organism susceptible in most cases to amoxicillin alone. 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 (β-lactamase producers), in acute otitis media was deemed appropriate.

Intended Use (from original 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≥2 mcg/mL) or beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* is suspected.

Primary Objective (from protocol)
- To obtain bacteriological efficacy data for *Augmentin* ES in the treatment of children with AOM due to *S. pneumoniae* with penicillin MICs of ≥ 2.0 mcg/mL
- To obtain bacteriological efficacy data for *Augmentin* ES in the treatment of children with AOM due to *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4.0 mcg/mL.

Secondary Objectives
- Demonstration of the clinical efficacy of *Augmentin* ES in patients infected with *S. pneumoniae* including isolates with amoxicillin/clavulanic acid MICs of 4.0 mcg/mL and in patients infected with *S. pneumoniae* including isolates with penicillin MICs of ≥ 2.0 mcg/mL.
- Assessment of the clinical and bacteriological efficacy of *Augmentin* ES in patients with AOM due to any pathogen.
- Determination of the incidence of adverse experiences (AEs), in particular diarrhea, in patients receiving *Augmentin* ES 90/6.4 mg/kg/day in divided doses q12h, for 10 days.

Inclusion Criteria
- 3 to 48 months of age with acute otitis media, diagnosed on the basis of otoscopic findings as either:

  1) purulent otorrhea of less than 24 hours duration,

  OR

  2) middle ear effusion (MEE) as evidenced by at least two of the following:

     a) decreased or absent tympanic mobility measured by pneumatic otoscopy
     b) yellow or white discoloration of the tympanic membrane (TM)
     c) opacification of the TM

  PLUS

  acute inflammation as evidenced by at least one of the following:

a ear pain within 24 hours, including patients presenting with unaccustomed tugging or rubbing of the ear
b marked redness of the TM
c distinct fullness or bulging of the TM

Medical reviewer's comments:
The reviewer applied the Divisional inclusion criteria. A full or bulging TM is usually associated with the presence of an acute ear infection. In the article entitled "Otitis Media: Can clinical findings predict bacterial or viral etiology?", the authors conclude that the single most important clinical feature associated with a pathogen infecting the middle ear was fullness and bulging of the TM; erythema was a less helpful indicator (McCormick et al, PIDJ 2000; 19: 256-8).

Exclusion Criteria

- Weighed more than 40 kg.
- Spontaneous perforation of the TM and drainage for longer than 24 hours.
- Tympanostomy tube(s) in place in the infected ear(s), or had anatomic abnormalities associated with prolonged MEE
- History of immune dysfunction/deficiency and those who had received immunosuppressive therapy; pediatric HIV patients without a clinical diagnosis of AIDS may have been enrolled if other study criteria were met.
- previous hypersensitivity reaction to penicillins, cephalosporins or other beta-lactam antibiotics, or an intolerance to *Augmentin.*
- Currently receiving or had received >1 dose of systemic antibiotic therapy within 72 hours prior to the initiation of the study; the exception was patients who had developed AOM while taking antimicrobial prophylactic therapy with either amoxicillin, erythromycin, sulfisoxazole, or trimethoprim/sulfamethoxazole.

Medical reviewer's comments:
Although Divisional guidelines suggest no systemic antibiotics for 72 hours or more before enrollment in the microbiologic study, and exclusion of patients with history of prophylaxis for recurrent OM, the reviewer accepted these patients to help enrich the population with patients who were more likely to have had penicillin resistant Streptococcus pneumoniae at study entry.

Prior and Concomitant Medication

During the course of the trial, concomitant medications necessary for the health of the patient were permitted, except for additional antimicrobial therapy (ophthalmic or topical antibiotics were permitted). Concomitant use of oral/nasal antihistamines, decongestants, and/or nasal steroids was permitted prior to and during the course of the study. Tubular secretion inhibitors (*e.g.*, probenecid) were prohibited.

Patients who received therapeutic doses of alternate antibiotics because of no improvement, worsening, or recurrence of signs and symptoms of AOM were, by definition, "clinical failures" at the next assessment (i.e., end of treatment and/or test of cure). Patients who received additional antibiotics any time before the test-

of-cure evaluation (day 25-28) for indications other than AOM were considered protocol violators and were not included in the per protocol population, but only in the intent-to-treat population.

Medical reviewer's comments:
The reviewer considered patients treated for persistent signs and symptoms of acute otitis media clinical failures, with presumed bacteriologic persistence, unless the patient had a repeat tympanocentesis to document otherwise.

Study Procedures

Outline of Study Assessments

Study Procedure / Visit	Preliminary Visit	On-Therapy Trtmnt	End-of-Cure Visit	Test-of-Visit
Visit No.	1	2	3	4
Day	(1)	(4- 6)	(12-15)	(25-28)
Written, Dated Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical History/Physical Exam.	X			
Baseline Signs/Symptoms	X			
Otological Assessment	X		X	X
Tympanocentesis/Bacteriology	X#	X*	*	*
Clinical Assessment	X	X	X	X
Adverse Experiences		X	X	X
Prior/Concomitant Medication	X	X	X	X
Assessment of Study Drug Compliance		X	X	

Source: Appendix A (protocol and sample CRF)

Note: If there was no improvement or if there was significant worsening of signs and symptoms of AOM, the patient was to return for an unscheduled interim visit which may have occurred any time between the preliminary and test-of-cure visit.
If tympanocentesis was performed within 24 hours of study entry a middle ear fluid specimen from this procedure was used for baseline bacteriology.

- Second tympanocentesis required at Day 4-6 for patients with baseline *S. pneumoniae*. Patients with other pathogens may have undergone 2nd tympanocentesis at this visit OR when deemed a treatment failure.
-

Baseline Phase

The investigator made a clinical diagnosis of AOM using otoscopic findings of either purulent otorrhea or MEE (two or more signs) with one or more signs of acute inflammation. Tympanocentesis, with culture of middle ear fluid (MEF), was performed on eligible patients with an intact TM at the preliminary visit. If the membrane was ruptured with purulent effusion of less than 24 hours duration, a direct culture was obtained.

On-Therapy Evaluation (Day 4-6)

An on-therapy assessment was required on day 4 to 6 after the start of study medication following a minimum of 3 full days of study medication (*i.e.*, 6 doses of *Augmentin* ES). If *S. pneumoniae* (alone or with other pathogens) was isolated at the preliminary visit, a second tympanocentesis was performed.

Sites could choose Option B, to perform a second tympanocentesis on patients from whom any pathogen had been isolated. If the patient's condition had not improved or had worsened, the patient was declared a clinical failure and was to be withdrawn from the study. For all withdrawn patients this visit then became the end-of-treatment evaluation. Patients withdrawn at this visit were required to attend the test-of-cure visit (day 25-28).

Interim Evaluation (optional)
An interim visit was scheduled if the patient showed no improvement, was significantly worsening, or had a recurrence of signs and symptoms of AOM between scheduled visits, at any time, from the preliminary visit to the test-of-cure visit. At the interim assessment, the investigator decided if it was necessary to withdraw the patient from or to continue the patient in the study.
A second tympanocentesis was not performed on patients who were withdrawn from the study prior to the on-therapy (day 4-6) evaluation, even if deemed a clinical failure.

End-of-Treatment Evaluation (Day 12-15)
The assessment of clinical response to therapy was made at this visit.
Clinical failure was defined as the patient's requirement for additional antibiotic therapy for AOM. The presence of MEE did not constitute clinical failure and should not have been treated with antibiotics during the study. Patients who were considered a "clinical failure" or "UTD" at the end of treatment, remained "clinical failure" or "UTD" respectively at the test-of-cure visit.

Medical reviewer's comments:
"UTD" refers to unable to determine.

Test-of-Cure Evaluation (Day 25-28)
All patients (including early failures/withdrawals) were to return for a scheduled test-of-cure visit on day 25-28. For early failures (i.e., prior to or at the end of treatment), this test-of-cure visit was solely a safety assessment and signs and symptoms were not recorded for patients who received additional antibiotics for the treatment of AOM.

Medical reviewer's comments:
The reviewer considered patients with recurrence of AOM between the EOT visit and the TOC visit failures. The reviewer based the assessment of the final clinical response to therapy on the results of this visit.

Bacteriological Assessment of Infection

Tympanocentesis was performed on all patients prior to administration of study medication (day 1). Tympanocentesis of the more symptomatic ear was performed on patients who presented with bilateral ear infections. If the patient had a ruptured tympanic membrane and purulent otorrhea of less than 24 hours duration, direct culture was obtained. Patients whose baseline MEF culture was sterile or which contained only commensal organisms were withdrawn from the study at the on-therapy visit without a repeat tympanocentesis. *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes*, and *Staphylococcus aureus* species were considered pathogens.

A second tympanocentesis was performed at day 4-6 on all patients who presented with *S. pneumoniae* (alone or with other pathogens) at the preliminary visit. For those patients who presented at the preliminary visit with other pathogens only, investigators chose from the following two options for the second tympanocentesis:

Option A: instances of treatment failure only

Option B: all patients at day 4-6

Investigators were to use the same option for all patients enrolled at their sites.

Medical reviewer's comments:

Divisional guidelines recommend that in cases of bilateral AOM, both ears should be tapped. However, since differences in the organisms cultured from both ears have been estimated to occur in about 5% of patients (Pelton et al. Am J Dis Child 1980;134:951-3), the reviewer accepted the applicant's plan to tap the more symptomatic ear in patients with bilateral AOM.

The reviewer inquired about the proposed management of patients in the S. pneumoniae group who failed after the second (on therapy) tap; the applicant's response was that only two taps were planned for this study. However, some investigators did perform a third tap on such patients.

Criteria for Inclusion in the Efficacy Analyses (taken from protocol, modified)

1. Per Protocol Population

To be included in any of the per protocol populations, a patient must have met all of the criteria listed below:

- a clinical diagnosis of AOM as defined in the protocol
- compliance with study medication must be 80% to 120% up to the time of withdrawal or study completion.
- must not have received any prohibited medication as defined in the protocol.
- received at least three full days of study medication

Medical reviewer's comments:
In addition to the evaluability criteria outlined above, the reviewer considered patients evaluable for the per protocol analysis if:

- *Divisional criteria for the diagnosis of AOM were met.*
- *Pretherapy tap was positive for pathogenic bacteria.*
- *Pretherapy culture of ear drainage (otorrhea) was positive for pathogen(s) of interest (Streptococcus pneumoniae, H influenzae, Moraxella catarrhalis, S. pyogenes)*
- *Patient returned for TOC visit, unless declared a failure before TOC visit.*
- *Prohibited medications, including oral steroids within 24 hours of study or injection of other steroids within 30 days, were not given.*
- *not withdrawn or lost to follow-up before the TOC visit (except clinical failures)*
- *withdrawn for adverse events before receiving 8 days or 16 doses of therapy were not evaluable for efficacy except clinical failures, for whom receipt of only 3 days of study drug was necessary*

Per protocol bacteriological *Streptococcus pneumoniae* population

- met all of the entry criteria
- had a baseline MEF culture positive for *S. pneumoniae* alone or *S. pneumoniae* plus other pathogens
- had a second tympanocentesis at days 4-6.

Per protocol other pathogens bacteriological population

- met all the entry criteria
- had a baseline MEF culture positive for *H. influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, or *Staphylococcus aureus* alone or in combination with other pathogen(s).

Per protocol clinical population at the test-of-cure visit

- had baseline, end-of-treatment, and test-of-cure clinical assessments.

Intent-to-Treat Populations (from protocol)
The clinical ITT population will include all patients who took at least one dose of study medication. The bacteriological ITT population will include all patients who took one dose of study medication and who had a tympanocentesis at entry.

Medical reviewer's comments:
The reviewer agrees with the definitions of the ITT populations.
The following patients were considered failures in the ITT population:

- *treated with concomitant antibiotics for an intercurrent illness not related to AOM*
- *treated for AOM during the follow-up period*
- *lost to follow-up*
- *consent withdrawn*
- *withdrawn for adverse event.*

A patient withdrawn for an adverse event who failed clinically before the adverse event occurred was considered evaluable in the per protocol population.
Patients not evaluable in all populations

- *did not have diagnosis of AOM at baseline*
- *Baseline middle ear fluid culture negative for bacterial pathogen(s)*
- *Received < 6 doses of study medication*
- *Non-compliant with study medication*

Endpoints
Primary Efficacy Parameter (taken from study report)
The primary efficacy parameter was the bacteriological response (bacteriological success or bacteriological failure) in patients with AOM due to *S. pneumoniae* with penicillin MICs ≥ 2 mcg/mL as well as the bacteriological response in patients with AOM due to *S. pneumoniae* with amoxicillin/ clavulanic acid MICs = 4.0 mcg/mL (in the PP bacteriological population at the on-therapy visit on Days 4, 5 or 6).
The bacteriological response is characterized by the following bacteriological outcomes:
Bacteriological Eradication: Eradication of *Streptococcus pneumoniae,* no fluid present.
Bacteriological Persistence: Non-elimination of *Streptococcus pneumoniae.*
Bacteriological Superinfection: Elimination of *Streptococcus pneumoniae* with the emergence of a new pathogen(s) with signs and symptoms of infection.
Unable to Determine: Bacteriological evaluation cannot be made (*e.g.,* sample lost, etc.)
A patient's bacteriological response will be defined as "success" if the bacteriological outcome is "bacteriological eradication" or "bacteriological superinfection"; "failure" is defined as a bacteriological outcome of "bacteriological persistence" or "unable to determine".

Medical reviewer's comments:
Consistent with Divisional guidelines, the reviewer based the determination of a primary bacteriologic outcome on the clinical response at the test of cure visit. (This comment was communicated to the applicant at the time of the review of the protocol prior to the initiation of the study).
The absence of a bacterial pathogen at the on therapy visit could not be taken to signify bacteriologic eradication; true bacterial eradication could be demonstrated only with a post treatment culture. Since post treatment bacteriologic specimens from the middle ear fluid were not routinely obtained in this study, eradication at the test of cure was presumed based on the clinical outcome.
Patients in whom the baseline pathogen was isolated on a repeat tap were considered bacteriologic failures. Patients who failed or relapsed clinically and did not have a repeat tympanocentesis (parents refuse, investigator fails to do, etc.) were presumed to

have bacteriologic persistence. Patients who failed clinically and had a repeat tympanocentesis, which showed no growth or growth of a different organism from that found at baseline, were considered bacteriologic successes.

Secondary Efficacy Variables (taken from protocol)
The secondary efficacy parameters evaluated will be: 1) bacteriological response of other pathogens to study medication at the on-therapy visit (day 4-6), and presumed bacteriological response of other pathogens to study medication at the end-of-treatment visit (day 12-15), 2) clinical response (clinical cure or clinical failure) at the end-of-treatment visit (day 12-15), and 3) clinical response (clinical cure, clinical failure, or clinical recurrence) at the test-of-cure visit (day 25-28).

At the test-of-cure evaluation (day 25-28), the investigator will determine whether a satisfactory response is maintained or a recurrence has developed, according to the following clinical outcomes:
Persistent Clinical Cure: Resolution of specific symptoms and otoscopic signs of acute infection for those patients who were clinically cured at the end of therapy such that no additional antibiotic therapy is prescribed for treatment of AOM.
Clinical Failure: Patients who were clinical failures at end of treatment such that additional antibiotic therapy is prescribed for treatment of AOM.
Clinical Recurrence: Reappearance of otoscopic signs and specific symptoms of acute infection for those patients who were clinically cured at the end of therapy and additional antibiotic therapy is prescribed for treatment of AOM.
Unable to Determine: A valid assessment of clinical outcome could not be made (i.e., patient does not return for follow-up visit).

A patient's clinical response will be defined as "success" if the clinical outcome is "persistent clinical cure", or as "failure" if the clinical outcome is "clinical failure", "clinical recurrence" (or "unable to determine" for intent-to-treat analysis). A patient deemed a failure at the end-of-treatment visit will be defined as a failure at the test-of-cure visit.
Medical reviewer's comments:
The reviewer assessed the clinical outcome at the TOC visit. Clinical failures in the per protocol population were defined as follows:

- *use of additional systemic antimicrobial agents needed to treat acute otitis media, or appearance of an intercurrent illness related to AOM, anytime between study initiation and TOC visit*
- *AOM with lack of improvement or worsening after 6 consecutive doses of study therapy as long as the other evaluability criteria were met*
- *Patients prematurely terminated for insufficient therapeutic response or adverse events related to AOM, as long as at least 6 doses of study drug were received at the time of termination*

All clinical failures were carried forward to subsequent visit(s) and to the test of cure visit; recurrences at the TOC visit were considered failures and were combined with prior failures for the overall assessment of clinical response at the test of cure visit.

Methods of Analysis (taken from protocol)
The on-therapy bacteriological response, end-of-treatment presumptive bacteriological response, end-of-treatment clinical response and test-of-cure clinical response determinations were tabulated by center and overall using descriptive statistics. Analysis of bacteriology data was based upon the per protocol population only.
Pathogens isolated from the tympanocentesis procedure were analyzed using descriptive statistics. The relative frequency of these pathogens and their susceptibilities were reported for all patients.

Planned Safety Evaluations (from protocol)
Protocol-Defined Diarrhea
Protocol-defined (PDD) diarrhea will be determined from the information recorded on the Patient Diary and is defined as follows:
• three or more watery stools in one day
OR
• two watery stools per day for two consecutive days
Patients who withdraw due to diarrhea or have a documented serious AE of diarrhea will be considered to have fulfilled the criteria for PDD and will therefore be analyzed as such even in the absence of diarrhea documented in the Patient Diary.

Medical reviewer's comments:
The reviewer accepted the applicant's definition of PDD; in addition, the reviewer considered patients with multiple loose stools in the assessment of safety.

Study dates:
24 February, 1999 to November 5, 1999

Investigators/Sites

Site No.	Investigator	Affiliation or Address	Location
Dominican Republic			
640	Dr. Jesus M. Feris Iglesias	Abraham Lincoln #2, Centro de Los Heroes	Santo Domingo
Costa Rica			
641	Adriano Arguedas Mohs, MD	Hospital Nacional De Ninos	San Jose
Guatemala			
642	Dr. Adib F. Rodriguez Solares	18 Avenida 18-77, Zona 10	Guatemala City
Israel			
600	Ronald Dagan, MD	Soroka University Medical Center	Beer-Sheva

United States

601	Amina Ahmed, M.D.	Carolinas Medical Center	Charlotte NC
602	Antonio Arrieta, M.D.	Children's Hospital Of Orange County	Orange CA
603	Susan A Carlin, M.D.	MetroHealth Medical Center	Cleveland OH
603	Mary Kumar, M.D.	MetroHealth Medical Center	Cleveland OH
604	Steven A. Chartrand, M.D.	Creighton University Medical Center	Omaha NE
605	Tasnee Chonmaitree, M.D.	University Of Texas Medical Branch At Galveston	Galveston TX
606	W. Manford Gooch III, M.D.	Hill Top Research / MRA	Salt Lake City UT
607	Joseph Haddad, Jr., M.D.	Columbia-Presbyterian Medical Center	New York NY
608	Alejandro Hoberman, M.D.	Children's Hospital Of Pittsburgh	Pittsburgh PA
609	Candice Johnson, M.D.	The Children's Hospital, Child Health Clinic	Denver CO
610	John E. McClay, M.D.	University Of Texas Southwestern Medical School	Dallas TX
611	Samuel E. McLinn, M.D.	Scottsdale Pediatrics Center	Scottsdale AZ
612	Mark L. Nichols, M.D.	Houston Ears, Nose And Throat Clinic (HENT)	Houston TX
613	Michael E Pichichero, M.D.	Elmwood Pediatric Group	Rochester NY
615	Richard Schwartz, M.D.	410 Maple Avenue West	Vienna VA
620	Lori E. Patterson, M.D.	East Tennessee Children's Hopsital	Knoxville TN
621	Gerson H. Aronovitz, M.D.	2714 Clairmont Road, NE	Atlanta GA
622	Colin Marchant, M.D.	Boston Medical Center	Boston MA
623	Harlan R. Muntz, M.D.	St. Louis Children's Hospital	St. Louis MO
627	Joseph A. Bocchini, Jr., M.D.	Louisiana State U. Medical Center	Shreveport LA
628	Randolph Richards, M.D.	Murfreesboro Medical Clinic	Murfreesboro TN
629	Raymond Rosenberg, M.D.	Northlake Pediatric Associates	Stone Mountain GA

Medical reviewer's comments:
The US sites are adequately distributed throughout the country.

STUDY RESULTS

Protocol Violations/Deviations (from study report)

In the Guatemala and Costa Rica sites, although the protocol states that patients with a sterile culture at baseline would be discontinued, these patients were treated for 10 days with Augmentin. No protocol amendment was submitted for this change in proposed plan.

Medical reviewer's comments:
The reviewer has presented only a part of the section entitled " Protocol Violations/ Deviations" from the study report because the applicant has not revised this section

following the discovery of the programming error. The results presented in this review represent those from the revised analyses by the applicant and the FDA reviewers.

Review of CRFs

In general, the Divisional evaluability criteria and outcome definitions were applied in the review of this study. Where the data were insufficient/ incomplete or discrepant, additional data or clarifications were requested from the applicant.

1. *Hard copies of the CRFs were not available to the reviewer because the applicant considered the eCRFs the source documents.*
2. *Bacteriologic results, not provided with the CRFs, were requested and received from the applicant.*
3. *The 162 patients without a baseline pathogen and the two patients without a clinical diagnosis of AOM at baseline (602-60080 and 602-60087) were not evaluable clinically or bacteriologically in the applicant's per protocol population. Consistent with the protocol, most patients without a baseline pathogen were withdrawn from the study between days 4 and 8. However, most continued to receive study medication for up to 10 days. Although the applicant notes that this occurred in Guatemala and Costa Rica, the database indicates that this occurred at other sites as well. No rationale has been provided for the continued treatment of these patients. However, the reviewer noticed a note in patient 603-60161's CRF, which states that it was decided (at investigators' meeting), before study initiation that patients would stay on study medication after withdrawal.*
4. *During the review of the CRFs of patients with S. pneumoniae at baseline, the reviewer noted that there were patients who had received concomitant antibiotics for failure/relapse but were considered non-evaluable by the applicant. The statistician determined that 69 patients fell into this group. The medical reviewer and statistician consider these patients evaluable failures. Following investigation of this question, the applicant acknowledged that there was a "processing error" and the revised analysis was submitted 2 weeks before the due date for an action on the NDA.*
5. *The reviewer noted that the investigator at site 600, (Israeli site) had tapped both ears in patients with bilateral AOM. This protocol deviation was not reported in the submission. It was not clear to the reviewer how the applicant decided results to include in the analysis. The applicant noted that an "arbitrary scheme for which ear was to be followed in the protocol" was devised by the investigator. However, the use of this arbitrary scheme does not address discordant results at baseline and on follow-up taps. For example, patient 600-59986 had bilateral taps at baseline and was retapped in both ears at the on therapy visit. The result from the right ear was no growth; however, S. pneumoniae, with sensitivities which appear similar to those at baseline, was regrown from the left ear. However, because the investigator had decided arbitrarily that the right ear was the ear of record for the study, the results from the left ear at baseline and at follow-up were not considered in the assessment of bacteriologic outcome.*

Patients whose evaluability/outcome were reassigned by the reviewer
PRSP population

600-00679
The applicant declared patient evaluable cure; the reviewer noted signs and symptoms of acute otitis media at the on therapy visit (d5-MEEs, redness, otalgia, bulging TMs bilaterally); deemed the patient an evaluable failure. Because the patient was an evaluable cure in the applicant's per protocol population, no additional antibiotics were administered.

600-59939
The investigator declared the patient a failure at d10; no concomitant medication was given; developed fever and leukocytosis on d24 for which concomitant antibiotics were given.
Applicant declared patient non-evaluable for receipt of concomitant antibiotics; deemed evaluable failure by reviewer for failure at d10, 2 weeks before concomitant antibiotics were given for another illness

601-60020
Patient seen by private physician d17 and concomitant antibiotics given for ear pain and acute otitis media; patient considered not evaluable by the applicant for missing the EOT visit; deemed evaluable failure by reviewer

602-60078
The applicant declared patient evaluable cure; the reviewer noted signs and symptoms of acute otitis media at the on therapy visit (d4-persistence of purulent otorrhea from R ear); patient deemed evaluable failure. Because the patient was an evaluable cure in the applicant's per protocol population, no additional antibiotics were administered.

604-60226
Patient declared evaluable cure by the applicant; the patient met protocol defined AOM at the TOC visit (bulging R TM and R MEE); deemed evaluable failure by the reviewer Because the patient was an evaluable cure in the applicant's per protocol population, no additional antibiotics were administered.

605-60305
Patient declared evaluable cure by the applicant; the patient met protocol defined AOM at the TOC visit (L TM red and MEE); deemed evaluable failure by the reviewer Because the patient was an evaluable cure in the applicant's per protocol population, no additional antibiotics were administered.
605-60306
Patient deemed clinical failure by investigator on d6 and withdrawn for "insufficient therapeutic effect"; concomitant antibiotics given
Patient declared not evaluable by applicant; deemed evaluable failure by reviewer

600-59953
Patient was declared clinical cure by investigator at EOT (d12); on d14, the investigator determined that the patient was a clinical recurrence and a 3rd tap was done and concomitant antibiotics given; results from third tap were consistent with bacteriologic failure (S. pneumoniae recultured); patient did not return for TOC visit
The reviewer considers this patient a clinical and bacteriologic failure; the applicant considered patient not evaluable.
Note: information regarding the course of illness for this patient was discovered after a query from the reviewer regarding the need for the 3rd tap. Because the response was received after the analysis had been completed, this patient has not been included as a clinical or bacteriologic failure in the results.

600-59986
Patient was a clinical failure at TOC (SB and FDA)
S. pneumoniae isolate from baseline regrew in left ear at the d4 tap-bacteriologic failure for reviewer; declared bacteriologic eradication by applicant; the reviewer considers this patient a bacteriologic and clinical failure.

7 patients were terminated from the study for insufficient treatment effect.
605-60306
Considered clinical failure by investigator on d6 and withdrawn for "insufficient therapeutic effect"; concomitant antibiotics given.
Patient declared not evaluable by applicant; deemed evaluable failure by reviewer
Note: this patient is in the PRSP population

606-60407
No baseline pathogen isolated; withdrawn d6 for insufficient therapeutic effect.
Bilateral tympanostomy placed on d9 for persistent OM; concomitant antibiotic d10 for prophylaxis for tympanostomy tubes; reviewer agrees that this patient is not evaluable for lack of a baseline pathogen.

608-60541
Patient considered clinical failure by the investigator at d5 and a second tap was done; patient withdrawn from the study d5 for " insufficient therapeutic effect" but study medication was continued; given concomitant antibiotic d13 for relapse of otitis media and again at test of cure visit for failure.
Reviewer considers patient evaluable failure; applicant considered the patient not evaluable for missed follow-up visits.

608-60578
Withdrawn for insufficient therapeutic effect d11; concomitant antibiotics given d11 and d14
Reviewer and applicant considered patient an evaluable failure.
Note: patient had S. pneumoniae at baseline but penicillin susceptibilities were not available

628-62030
Withdrawn for insufficient therapeutic effect on d9; patient is non-evaluable per applicant for missed follow-up visits, but considered evaluable clinical failure by the reviewer.

628-62031
Clinical failure per investigator at EOT visit, d14; no concomitant antibiotics given; patient withdrawn for insufficient therapeutic effect d14.
Applicant considered this patient not evaluable for missed TOC visit; however, since patient failed at EOT visit, reviewer deemed patient an evaluable clinical failure and carried forward to the TOC.

628-62033
Patient withdrawn d4 for insufficient therapeutic effect
No pathogen at baseline; reviewer agrees with applicant that this patient is not evaluable

Medical reviewer's comments:
Four patients--605-60306, 608-60541, 628-62030, 628-62031--were still being excluded from the applicant's revised per protocol population for missing EOT and/or TOC visits, even though these patients were discontinued for failure. Because the company's revised analysis was received so close to the due date, there was not sufficient time to review all patients in the FDA data set. Unidentified problems may still persist in the revised analysis; however, the revised results reported for the PRSP population have been reviewed and are acceptable.

PATIENT DISPOSITION AND EVALUBILITY

Table 1 The Number of Patients Enrolled by Center, Completed the Study and Valid for Bacteriologic Efficacy (applicant's table)

		Completed		Valid for Per-Protocol S.Pneumoniae Analysis	
Center	Randomized	n	(%)	n	(%)
Overall	521	305	(58.5%)	119	(22.8%)
600	125	82	(65.6%)	38	(30.4%)
601	21	9	(42.9%)	2	(9.5%)
602	21	13	(61.9%)	6	(28.6%)
603	12	3	(25.0%)	2	(16.7%)
604	2	2	(100.0%)	1	(50.0%)
605	7	6	(85.7%)	3	(42.9%)
606	36	15	(41.7%)	1	(2.8%)
607	1	0		0	
608	85	53	(62.4%)	13	(15.3%)
609	24	14	(58.3%)	5	(20.8%)
610	2	2	(100.0%)	1	(50.0%)
611	10	10	(100.0%)	6	(60.0%)
612	4	3	(75.0%)	0	
613	3	3	(100.0%)	0	
615	24	13	(54.2%)	5	(20.8%)

620	2	2	(100.0%)	0	
621	10	8	(80.0%)	4	(40.0%)
622	1	0		0	
623	2	1	(50.0%)	1	(50.0%)
627	3	1	(33.3%)	1	(33.3%)
628	9	2	(22.2%)	1	(11.1%)
629	1	1	(100.0%)	0	
640	27	18	(66.7%)	7	(25.9%)
641	50	27	(54.0%)	14	(28.0%)
642	39	17	(43.6%)	8	(20.5%)

Medical reviewer's comments:
The 4 foreign sites are sites 600, and sites 640-642. Site 600 randomized approximately 125 (24%) of the total patients in the study. Of the 305 patients that completed the study, 144 (47.2%) were participants in the foreign sites.
The numbers of patients valid for the sponsor's per-protocol S. pneumoniae analysis in the table do not reflect the addition of patients back into the per protocol population which resulted from the revisions to the analysis. The applicant has been asked to revise the study report accordingly.

Table 2 Number (%) of Patients Who Completed the Study or Withdrew from the Study, by Reason for Withdrawal (applicant's table, modified)

	Augmentin ES N=521 N (%)
Completed the Study	305 (58.5)
Total Withdrawal	216 (41.5)
Sterile MEF at Baseline	136 (26.1)
Lost to follow-up	28 (5.4)
Adverse experiences	25 (4.8)
Other*	10 (1.9)
Insufficient therapeutic effect	7
Protocol deviation**	7 (1.3)

* Includes non-compliance, missed visits, failure to meet inclusion/exclusion criteria and lack of laboratory results.
** Including non-compliance.

Source: Table 7 from study report

Medical reviewer's comments:
The applicant's table indicates that 216 patients were withdrawn from the study, but the table accounts for only 213 patients. In the reviewer's table which follows, the total number of withdrawals is 216 and the distribution of patients, based on the reason for withdrawal, differs from that of the applicant.

Table 3 Reasons for withdrawal (MO)

	Augmentin ES N= 521	
	n	(%)
Completed the Study	305	(58.5)
Total Withdrawal	216	(41.5)
Sterile MEF at Baseline	162	(31.1)
Lost to follow-up	16	(3.1)
Adverse experiences	18	(3.5)
Other*	10	(1.9)
Insufficient therapeutic effect	5	(1.3)
Protocol deviation**	5	(0.96)

* Includes non-compliance, missed visits, failure to meet inclusion/exclusion criteria and lack of laboratory results.
** Including non-compliance.

Medical reviewer's comments:
Seventy five percent (126/216) of the patients were withdrawn for the lack of a baseline bacterial pathogen. Note that the number of patients withdrawn for lack of a baseline pathogen differs from that in the applicant's table. The reviewer derived 162 from querying the applicant's electronic database and master variables listing. In addition, section 4.3 of the study report entitled "Protocol violations"; the applicant notes that 359/521 patients had a baseline pathogen, i.e., 162 did not have a baseline pathogen.

Table 4 ITT and Per-Protocol Bacteriological Populations, modified

	Augmentin ES N=521			
Bacteriological ITT	n/N		(%)	
	359/521		(68.9)	
	ITT		Per Protocol	
Bacteriological Populations	N/N	(%)	n/N	(%)
S. pneumoniae alone or with other pathogens	157/359	(43.7)	123/157	(78.3)
S. pneumoniae alone or with other pathogens (Penicillin MICs ≥2.0 mcg/mL)	41/157	(26.1)	33/41	(80.5)
Other/Multiple pathogens	246/359	(68.5)	188/246	(76.4)

Medical reviewer's comments:
The bacteriologic ITT population consisted of patients with a baseline pathogen. Forty-one patients had S. pneumoniae with penicillin MIC≥2μg/mL at baseline.

Table 5 Clinical Populations, applicant's table modified

	Augmentin ES N=521	
Clinical Populations	**n/N**	
Clinical ITT	521/521	
Per Protocol Populations		
Clinical Population End of Therapy	300/521	
Clinical Population Test of Cure	289/521	
Protocol Defined Diarrhea Evaluable Population	497/521	
Clinical Population at End of Therapy Baseline characteristic: Patients with *S. pneumoniae*	**ITT** **n/N**	**(%)**
S. pneumoniae alone or with other pathogens	157/521	(30.1)
S. pneumoniae alone or with other pathogens (Penicillin MICs ≥2.0 mcg/mL)*	41/157	(26.1)
S. pneumoniae alone or with other pathogens (Penicillin MICs < 2.0 mcg/mL)*	109/157	(69.4)

* Seven patients (six of whom were in the PP bacteriological population) had no baseline penicillin MICs. These patients were excluded from all presentations based on penicillin MICs.

Medical reviewer's comments:
As noted previously, because some patients were put back into the efficacy per-protocol population following the discovery of the programming error, the numbers will differ from those presented in this table. The applicant has been asked to revise the study report accordingly.

DEMOGRAPHICS

Table 6 Demographic Characteristics - ITT Population, modified

Demographic Characteristics	*Augmentin* ES N=521	
Gender, n (%)		
Male	312	(59.9)
Female	209	(40.1)
Race, n (%)		
Caucasian	311	(59.7)
Black	90	(17.3)
Oriental	1	(0.2)
Other	119	(22.8)
Age (mos)		
Mean (SD)	18.59 (12.01)	
Median	14.37	
Min-Max	(3.1, 50.9)	
Weight (kg)		
Mean (SD)	10.83 (3.11)	
Median	10.2	
Min-Max	(4.5, 25.4)	

Source: Table 10 from study report

Medical reviewer's comments:
Sixty percent of the patients were male and white; only 17% of the patients were black. The mean age was approximately 18.6 months of age. The majority of patients classified as "Other" were Hispanic patients from the Central American sites.

BASELINE CHARACTERISTICS

Table 7: Baseline characteristics of patients with a baseline pathogen

Attribute	ITT: Baseline Pathogen		ITT:SP		ITT:PRSP		FDA Clinical PP: PRSP	
	Rate	N	Rate	N	Rate	N	Rate	N
S. pneumoniae documented	0.437	359	1.000	157	1.000	41	1.000	33
PRSP documented	0.114	359	0.261	157	1.000	41	1.000	33
>1 pathogen documented	0.139	359	0.280	157	0.390	41	0.485	33
Purulence	0.072	359	0.089	157	0.122	41	0.152	33
Abnormal mobility	0.980	343	0.987	149	0.949	39	0.935	31
Abnormal color	0.989	355	0.993	153	0.974	39	0.968	31
Abnormal opacity	0.983	354	0.980	153	0.949	39	0.935	31
Otalgia	0.848	355	0.840	156	0.805	41	0.788	33
Redness	0.868	355	0.863	153	0.846	39	0.806	31
Abnormal position	0.943	351	0.928	152	0.923	39	0.903	31
USA center	0.526	359	0.484	157	0.537	41	0.576	33
Antibiotics previous 3 months	0.530	285	0.521	121	0.808	26	0.773	22
Day care	0.404	285	0.405	121	0.462	26	0.409	22
Age > 18 months	0.354	359	0.357	157	0.220	41	0.242	33
Temperature > 98.6	0.666	338	0.730	152	0.675	40	0.719	32
Male sex	0.593	359	0.561	157	0.561	41	0.515	33

SP=*S. pneumoniae*; PRSP=penicillin resistant *S. pneumoniae*

Medical reviewer's comments:
One hundred sixty two patients did not have a baseline pathogen (results not shown in the table). Of these 162, almost half (47%) were older than 18 months of age, 45% had received antibiotics in the previous 3 months, and one third attended day care.
In patients with a baseline pathogen (ITT, n=359), approximately half had received antibiotics within the previous 3 months, 40.4% were in day care, 65% were under 18 months of age, and less than 1% (26 patients) had purulent otorrhea. Forty four percent of these patients in the ITT population (n=359) had S. pneumoniae at baseline (alone or with another pathogen).
In the penicillin resistant S. pneumoniae ITT population (n=41), 81% of patients had received antibiotics in the previous 3 months, approximately half were in daycare, 78% were less than 18 months of age and 54% were less than 12 months of age.
Since penicillin resistant S. pneumoniae (PRSP) was the pathogen of interest, the results and comments which follow will focus on the PRSP population(n=41). Results for S. pneumoniae with amoxicillin MIC=4 µg/mL are not presented or discussed since the applicant seeks an indication for penicillin resistant S. pneumoniae only at this time.

Table 8 Differences in Assignment of Clinical Outcome at TOC-FDA for patients with AOM due to PRSP (MIC≥2μg/mL) (MO table)

	FDA	Sponsor
Success	14	18
Fail	20	12
Indeterminate	7	11
Total	41	41

Table 9 Account of differences in assignment of clinical failure at TOC in the PRSP (MIC=2μg/mL) (MO table)

	FDA	Sponsor
Concomitant antibiotic for AOM relapse	12	12
Concomitant antibiotic for failure, TOC missed 600-59953 601-60020 605-60306	3	0
Concomitant antibiotic after failure for intercurrent illness 600-59939	1	0
Protocol defined AOM at TOC 604-60226 605-60305	2	0
Consistent with failure at on therapy visit 600-00679 602-60078	2	0

Reviewer's comments:
As summarized above, the reviewer had eight additional failures --four patients called successes and four patients called indeterminate by the applicant. Of the 20 patients considered failures by the reviewer, 11 (55%) failed ≤7 days after the completion of study drug. Eleven patients (55%) had penicillin MIC= 2μg/mL and 9 had penicillin MIC= 4μg/mL at baseline. Eleven patients (55%) were ≤12 months of age, whereas the mean and median ages for the total study population were 18.6 and 14.4 months of age, respectively.
Because information about patient 600-59953's full clinical course was not available to the FDA reviewers until late, this patient has not been included in the main tables of the FDA's efficacy analysis which rely on the sponsor's revised analysis.

CLINICAL OUTCOME

Table 10 Clinical outcome at TOC for different populations– revised sponsor data (FDA table)

Population	ITT (Missing count as failures)				PP			
	Sponsor		FDA		Sponsor		FDA	
	N	Rate	N	Rate	N	Rate	N	Rate
Baseline Pathogen	359	0.627	359	0.607	289	0.723	295	0.685
S. pneumoniae	157	0.675	157	0.637	131	0.756	135	0.689
S. pneumoniae Penicillin MIC<2	109	0.752	109	0.734	94	0.809	95	0.779
S. pneumoniae Penicillin MIC≥2*	41	0.463	41	0.366	30	0.600	33	0.424
S. pneumoniae Penicillin MIC=2	23	0.478	23	0.391	19	0.579	20	0.450
S. pneumoniae Penicillin MIC=4*	18	0.444	18	0.333	11	0.636	13	0.385
H. influenzae	197	0.594	197	0.594	154	0.688	156	0.679
M. catarrhalis	29	0.483	29	0.483	25	0.560	25	0.560
S. pyogenes	16	0.813	16	0.750	14	0.857	14	0.786
S. aureus	12	0.667	12	0.667	11	0.727	12	0.667

*PID=536.600.59953 was not included in the FDA PP. However, the patient should have been classified as a clinical failure in the per protocol population at the TOC.

Medical reviewer's comments:
Although the clinical responses were 69% for the overall S. pneumoniae population and 78% for the penicillin susceptible S. pneumoniae patients, respectively. The results for patients in the PRSP population are summarized in the table which follows.

Table 11 Clinical outcome at TOC for PRSP population

Population	ITT (Missing count as failures)				PP			
	Sponsor		FDA		Sponsor		FDA	
	N	Rate	N	Rate	N	Rate	N	Rate
S. pneumoniae Penicillin MIC≥2 $\mu g/mL$ *	41	0.463	41	0.366	30	0.600	33	0.424
S. pneumoniae Penicillin MIC=2 $\mu g/mL$	23	0.478	23	0.391	19	0.579	20	0.450
S. pneumoniae Penicillin MIC=4 $\mu g/mL$ *	18	0.444	18	0.333	11	0.636	13	0.385

*PID=536.600.59953 was not included in the FDA PP.

Medical reviewer's comments:
The clinical response in patients with PRSP was 42.5% in the FDA per protocol analysis (41.2% with the inclusion of patient 600-59953 as a failure). Patients with S. pneumoniae penicillin MIC=4μg/mL had a worse clinical outcome than patients with S. pneumoniae penicillin MIC=2μg/mL, 38.5% (35.7% with patient 600-59953) vs. 45%, respectively.

Table 12 FDA clinical outcome for PRSP populations

Population	PRSP		PRSP (MIC=2)		PRSP (MIC=4)	
	N	Success Rate	N	Success Rate	N	Success Rate
ITT (missing counted as failures)	41	.366	23	.391	18	.333
ITT (missing excluded)	37	.405	21	.429	16	.375
FDA PP plus patients withdrawn for AEs *	36	.389	21	.429	15	.333
FDA PP plus patient 600.59953** as a failure	34	.412	20	.450	14	.357
FDA PP	33	.424	20	.450	13	.385

*patients put on new antibiotic for AOM because of AE
**PID=536.600.59953--based on information provided by the sponsor late in the review period, the patient should have been classified as a clinical failure in the per protocol population at the TOC.

Medical reviewer's comments:
When the 4 patients called failures by the reviewer based on clinical presentation (604-60226, 805-60305, 600-00679, and 602-60078) were counted as cures (i.e., the sponsor's assignment of clinical outcome), the FDA optimistic clinical outcome for the PRSP population was 53% vs. 60% for the sponsor. The persistent difference in the optimistic clinical outcome can be accounted for by the 4 patients (600-59953, 601-60020, 605-60306, 600-59939) who received concomitant antibiotics but were still considered not evaluable in the applicant's revised per protocol population (and were counted as failures by the reviewer).
These results are summarized in the table below.

Table 13 "Optimistic" clinical outcome at TOC for penicillin resistant *S. pneumoniae* populations

Population	PRSP		PRSP (MIC=2)		PRSP (MIC=4)	
	N	Success Rate	N	Success Rate	N	Success Rate
FDA PP with **optimistic outcomes***	34	.529	20	.550	14	.500
Sponsor PP with **optimistic outcomes**	30	.600	19	.579	11	.636

* includes patient 600.59953 who is counted as a failure.

BACTERIOLOGICAL OUTCOME

Table 14 Study day 4-6 (on therapy) bacteriologic success rates for *S. pneumoniae* populations – revised sponsor data

Population	ITT		PP	
	n/N	(%)	n/N	(%)
S. pneumoniae (all)	149/157	(94.3)	121/123	(98.4)
S. pneumoniae Penicillin MIC<2μg/mL	103/109	(94.5)	84/84	(100)
S. pneumoniae Penicillin MIC=2μg/mL	22/23	(95.7)	19/19	(100)
S. pneumoniae Penicillin MIC=4μg/mL	16/18	(88.9)	12/14	(85.7)
S. pneumoniae Penicillin MIC≥2μg/mL	38/41	(92.7)	31/33	(93.9)

Medical reviewer's comments:
The bacteriologic responses at the on therapy visit were very high for all patients with S. pneumoniae in the per protocol and ITT populations; however, these results do not represent true eradication since the taps were done while the patients were still receiving study drug.
Overall bacteriologic and clinical outcome results are summarized in the table below. Seven patients were bacteriologic failures for regrowth of a baseline pathogen in the study; 5 were in the PRSP group and 2 were in the penicillin susceptible S. pneumoniae (PSSP) group. Time to declaration of failure is included in parentheses:
PRSP: 600-59953 (d14), 600-59986 (d4), 605-60306 (d6), 611-60756 (d4), 621-61505 (d20). Note that patient 611-60756 was declared a clinical cure at the TOC visit.
PSSP: 600-59966 (d4), 608-60540 (d14).

Table 15 FDA Bacteriologic and clinical efficacy outcomes for *S. pneumoniae* populations (Revised data)

Population	Assessment	ITT (missing counted as failures)				FDA PP			
		N	Success Rate	Exact 95% Confidence Interval		N	Success Rate	Exact 95% Confidence Interval	
				Lower	Upper			Lower	Upper
S. pneumoniae	Micro	157	0.943	0.894	0.973	123	0.984	0.942	0.998
	Clinical	157	0.637	0.556	0.712	135	0.689	0.604	0.766
PSSP	Micro	109	0.945	0.884	0.979	84	1.000	0.957	1.000
	Clinical	109	0.734	0.641	0.814	95	0.779	0.682	0.858
PRSP	Micro	41	0.927	0.801	0.985	33	0.939	0.798	0.993
	Clinical*	41	0.366	0.221	0.531	33	0.424	0.255	0.608
PRSP (MIC=2)	Micro	23	0.957	0.780	0.999	19	1.000	0.823	1.000
	Clinical*	23	0.391	0.197	0.615	20	0.450	0.231	0.685
PRSP (MIC=4)	Micro	18	0.889	0.653	0.986	14	0.857	0.572	0.982
	Clinical*	18	0.333	0.133	0.590	13	0.385	0.139	0.684

Micro= microbiologic outcome at Day 4-6; Clinical=clinical outcome at TOC
*Results do not include patient 600-59953 who should have been classified as a clinical failure in the per protocol population at the TOC.

Medical reviewer's comments:
Bacteriological outcomes for all S. pneumoniae populations, based on tympanocentesis results from the on therapy visit, were consistently higher (>85%) than with the corresponding clinical outcomes assessed off therapy at the test of cure visit. Recall that for the FDA analysis, the primary bacteriologic outcome was determined at the TOC visit and inferred from the clinical outcome at TOC.

VII. Safety

Deaths and Serious Adverse Events

There were no deaths reported during this study or for the 30 days following each patient's completion of this trial. Six patients were reported to have had at least one non-fatal, serious adverse experience at any time during the study. (The patient narratives are summarized in Appendix I). Diarrhea, the most frequently occurring serious adverse event (SAE) (0.4%; 2/521), was the only SAE reported by more than one patient.

Table 16 Number (%) of Patients Reporting Serious Adverse Experiences

	***Augmentin* ES**	
		N=521
AE by Body System/Preferred Term	**N**	**(%)**
Patients with Serious AEs	**6**	**(1.2)**
Gastrointestinal System	**3**	**(0.6)**
Diarrhea	2	(0.4)
Vomiting	1	(0.2)
Respiratory System	**2**	**(0.4)**
Asthma	1	(0.2)
Pneumonia	1	(0.2)
Body As A Whole	**1**	**(0.2)**
Increased Therapeutic Response (Overdose)	1	(0.2)
Metabolic and Nutritional	**1**	**(0.2)**
Dehydration	1	(0.2)

Source: Table 32 in study report

Medical reviewer's comments:
Of the 6 patients with serious adverse events, 4 had protocol defined diarrhea (see Appendix III). The 2 patients with asthma and pneumonia had watery stools but not protocol defined diarrhea during the study.

Table 17 Number (%) of Patients Reporting Adverse Experiences Leading to Withdrawal

	***Augmentin* ES**	
	N=521	
AE by Body System/Preferred Term	**N**	**(%)**
Patients With At Least One AE Leading To Withdrawal*	25	(4.8)
Gastrointestinal System	18	(3.5)
Diarrhea	15	(2.9)
Vomiting	7	(1.3)
Abdominal Pain	1	(0.2)
Melena	1	(0.2)
Skin and Appendages	4	(0.8)
Rash	2	(0.4)
Maculo-Papular Rash	1	(0.2)
Urticaria	1	(0.2)
Application Site	2	(0.4)
Contact Dermatitis	2	(0.4)
Resistance Mechanism	2	(0.4)
Infection	1	(0.2)

Otitis Media	1	(0.2)
Body As A Whole	1	(0.2)
Fever	1	(0.2)

*The number of patients within a body system are not additive since a patient can have more than one withdrawal reason within a Body System

Source: Table 33 in study report

Medical reviewer's comments:
Diarrhea was the most common reason for withdrawal; 15/25 (60%) patients were withdrawn for diarrhea. Vomiting was the second most common adverse event leading to withdrawal (7/25 patients). The patient listings for withdrawals are included as Appendix II.

Table 18 Number (%) of Patients with Protocol-Defined Diarrhea (PDD)

	***Augmentin* ES** N=521	
	n	**(%)**
Patients with PDD		
Yes	65	(12.5%)
No	456	(87.5)

Source: Table 35 in the study report

Medical reviewer's comments:
The listing of patients with PDD is included as Appendix III. Sixty-five patients were reported with protocol defined diarrhea (3 or more watery stools in a day, 2 watery stools on 2 consecutive days' or reported an adverse event of 'diarrhea). Five more patients---607-60451, 608-60560, 623-61651, 641-62552, and 641-62594--- were identified by the reviewer as being included in the applicant's database for PDD but not accounted for in the table above. Patient 641-62594 was hospitalized for diarrhea and dehydration (counted as SAE). The three sites with the largest enrollment, sites 600, 641, and 642 appeared to have low rates of diarrhea. The rate of PDD in this study is higher than that seen in the Augmentin 7:1 study (8.7 and 9.6% for patients who received Augmentin 7:1 for 5 days vs. 10 days, respectively).

	% PDD	**% withdrawals for diarrhea**
Augmentin 4:1vs. 7:1(10d)	26.7 vs. 9.6	7.6 vs. 3.1
Augmentin 14:1 vs. 7:1	12.6 vs. 10.8	
Augmentin 14:1 (study 536)	13.6	2.9

Medical reviewer's comments:
Several patients were reported with episodes of loose stools but they did not meet the protocol definition of diarrhea.

Table 19 Most Frequently Occurring (>1% of Patients) Adverse Experiences – ITT Population

	***Augmentin* ES N=521**	
Adverse Experience by Preferred Term	**n**	**(%)**
Patients Reporting At Least One AE	193	(37.0)
Vomiting	36	(6.9)
Contact Dermatitis*	32	(6.1)
Fever	32	(6.1)
Otitis Media**	23	(4.4)
Upper Respiratory Tract Infection	21	(4.0)
Diarrhea	20	(3.8)
Rhinitis	15	(2.9)
Earache	1	(0.2)
Rash	13	(2.5)
Coughing	12	(2.3)
Asthma	8	(1.5)
Moniliasis	8	(1.5)
Nervousness	7	(1.3)
Conjunctivitis	6	(1.2)
Toothache	6	(1.2)

Data Source: Section 12, Table 12.02, 12.04; Appendix D, Listings D.01(a) and D.01(b).
* Consisted of reports of diaper rash
** Includes recurrence of otitis media between EOT and TOC for patients with baseline pathogen and recurrence or persistence of otitis media at final safety assessment for patients with no baseline pathogen; Therefore, otitis media is not considered to be a potential side-effect of treatment with *Augmentin* ES.

Medical reviewer's comments:
Overall, vomiting appeared to be the most commonly occurring adverse event, followed by contact dermatitis (diaper rash) and fever.
The safety information from this study and the previously submitted clinical study with the 14:1 formulation were combined. The combined results (not shown) were essentially the same as those reported here for the single study.
The applicant also submitted a safety update report for ongoing studies with Augmentin 14:1 formulation. No deaths have been reported in the approximately 313 patients who have received the study drug these studies (reporting period cutoff date 5/31/2000). Results of serious adverse events and withdrawals for adverse events from these ongoing studies are summarized in the table below.

Table 20 Safety Update from Ongoing Studies with Augmentin ES (MO)

Study	No. enrolled	withdrawn for AE	w/d for diarrhea	serious AE
536	149	11(7.3)	5 (3.4)	6 (4.0)
541	56	5 (8.9)	4 (7.1)	0
555	~100	2 (2.0)	2 (2.0)	3 (3.0)
574	8	0	0	0
Total	~313	18 (5.6)	11 (3.5)	9 (2.9)

Medical reviewer's comments:
The rates of serious adverse events and adverse events leading to withdrawal are consistent with those seen for studies 447 and 536, submitted to support this application.

Conclusions

1. *The overall clinical response in patients with PRSP is 41.2% (CI 24.6%-59.3%) in the FDA per protocol analysis. When stratified according to the penicillin MIC, patients in the PRSP group with penicillin MIC=4μg/mL achieved a worse clinical response than those with penicillin MIC=2μg/mL.*

2. *The bacteriologic outcome at the on therapy visit was inconsistent with the clinical outcome at the test of cure visit.*

3. *No significant adverse events were noted.*

Recommendations

On the basis of the data submitted, Augmentin ES (90mg/kg/day; 14:1 formulation) has not been demonstrated to be effective in the treatment of acute otitis media due to penicillin resistant S. pneumoniae; therefore, NDA 50-755 is not recommended for approval.

/S/

Mamodikoe Makhene, M.D.
Medical Reviewer, HFD-520

NDA 50-755
HFD-520
HFD-520/DepDir/L Gavrilovich
HFD-520/MO/M Makhene
HFD-520/Chemistry/A Yu
HFD-520/Microbiology/S Altaie
HFD-520/Biopharmaceutics/F Pelsor
HFD-520/PM/S Samanta

Concurrence Only:
HFD-520/Acting DivDir/J Soreth
HFD-520/TmLdrMO/M Albuerne

/S/ 10/3/00

APPENDIX I

Patient 536.601.60021, a seven-month-old male with no significant medical history, received open label *Augmentin* ES from 10-Sep-1999 to 19-Sep-1999. On 03-Oct-1999, 15 days after the last dose of *Augmentin* ES, the patient was returning from vacation when he had an asthma attack. Intensity was reported as severe. The patient's mother took him to the hospital where he was admitted. He was released from the hospital on 05-Oct-1999. A follow-up visit indicated the patient had continued wheezing. The investigator indicated the patient had no prior history of asthma. Corrective therapy for asthma included albuterol. The investigator reported the asthma was unrelated to treatment with study medication.

Patient 536.602.60077, a 1-year-old male patient with a medical history which included reactive airway disease and acute gastroenteritis, received open-label *Augmentin* ES from 11-May-1999 to 21-May-1999. A second tympanocentesis done on 24-May-1999 grew *Streptococcus pneumoniae*. The patient was treated with Suprax (cefixime) from 24-May-1999 to 02-Jun-1999. The investigator reported this as a clinical failure at the end of therapy visit (24-May-1999). From 02-Jun-1999 to 03-Jun-1999 the patient was treated with a "high" (250 mg) dose of amoxicillin. On 03-Jun-1999, the patient's father indicated his son experienced three episodes of vomiting, intensity reported as moderate. The patient was admitted to the hospital in order to receive treatment with intramuscular ceftriaxone for presumed intolerance to oral medication. The event resolved and the patient was discharged from the hospital on 04-Jun-1999. The investigator
reported the vomiting to be unrelated to treatment with study medication, but probably associated with amoxicillin.

Patient number 536.602.60081, a 5-month-old male whose medical history included AOM, prematurity and jaundice, received *Augmentin* ES from 07-Jun-1999 to 17-Jun-1999. On 07-Jun-1999 the child was discharged home on the oral study medication. The mother reported the infant was doing well and was sleeping. An hour later, the infant refused to eat, was vomiting, was "acting worse", and somewhat more irritable. The patient was admitted to the hospital for acute otitis media, to rule out bacteremia or meningitis. A chest x-ray was positive for pneumonia. The event was reported as ongoing. The investigator reported the lower respiratory infection of moderate intensity and as not related to treatment with study medication but probably associated with viral pneumonia.

Patient number 536.602.60090, a 17-month-old female with a medical history of fever, vomiting and a decreased range of motion on the right shoulder, received treatment with open-label *Augmentin* ES from 19-July-1999 to 28-July-1999. During a routine monitoring visit, it was discovered the patient was dosed at 7.5 mLs twice daily for ten days based on the subject's weight of 10.1 kg. The patient should have received a dosage of 3.8 mLs twice a day for ten days. The investigator reported the patient received the study medication without any

complication. The overdose was noted as a pharmacy error. The investigator reported the mild overdose as unrelated to treatment with study medication.

Patient number 536.641.62594, a 15-month-old male with no significant medical history received treatment with open-label *Augmentin* ES from 26-Aug-1999 to 05-Sep-1999. On 06-Sep-1999 the patient experienced abundant watery stools that required hospitalization that same day. The patient was hospitalized due to dehydration and was treated with intravenous 5% dextrose in water plus electrolytes. The patient was discharged from the hospital 10-Sept-1999 with no diarrhea or dehydration and in excellent clinical condition. The investigator reported the mild diarrhea and moderate dehydration as suspected relation to treatment with study medication.

Patient number 536.642.62661, a 34 month-old male with a medical history which included constipation, croup, and a skin infection, received open label *Augmentin* ES from 26-Aug-1999 to 29-Aug-1999. On 28-Aug-1999 the patient experienced intermittent diarrhea (9 episodes). Treatment with study medication was stopped and the patient was withdrawn from the study. The investigator considered the diarrhea to be serious, (as a potentially significant hazard, contraindication, side effect or precaution that may have been associated with the use of the drug). The moderate diarrhea was reported to be probably related to treatment with open-label *Augmentin* ES.

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APPENDIX II

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Table Patients with Adverse Experiences Leading to Withdrawal at Any Time During the Study

			Augmentin ES			
PID	**AE Preferred Term Verbatim**	**Onset Day***	**Intensity**	**Relationship**	**Corrective Therapy**	**Comment**
536.600.00681	Infection/ Dysentery	6	Moderate	Unrelated	Yes	Corrective treatment for the dysentery was oral rehydration solution and ceftriaxone
536.600.00700	Rash, maculo-papular/ Maculo-papular rash	3	Moderate	Probable	No	
536.600.59924	Otitis Media/ Relapse of Left AOM	7	Moderate	Probable	Yes	Corrective treatment for the relapse included paracetamol and cefuroxime.
536.600.59945	Fever/ Fever	6	Moderate	Unrelated	Yes	Corrective treatment for the fever included ceftriaxone.
536.600.59966	Diarrhea/ Diarrhea	2	Severe	Probable	Yes	There were ten episodes of diarrhea over twelve days.
536.600.59967	Diarrhea/ Diarrhea	1	Moderate	Probable	No	
	Vomiting/ Vomiting	1	Severe	Probable	Yes	
536.600.59968	Diarrhea/ Diarrhea	1	Severe	Probable	No	
	Vomiting/ Vomiting	1	Moderate	Probable	Yes	
536.600.59983	Diarrhea/ Diarrhea	1	Moderate	Probable	No	There were five episodes of diarrhea over six days.
	Contact Dermatitis/ Diaper Rash	4	Severe	U unrelated		No
536.602.60085	Diarrhea/ Diarrhea	2	Severe	Probable	No	
	Rash/ Rash Around The Eyes	3	Mild	Unrelated	No	
536.602.60089	Diarrhea/ Diarrhea	10	Severe	Probable	No	
536.606.60396	Vomiting/ Vomiting	2	Mild	Suspected	No	
536.606.60402	Diarrhea/					Corrective treatment for the diarrhea included Pepto Bismol (bismuth subsalicylate) and

	Diarrhea	1	Moderate	Unrelated	Yes	Pediazole (acetyl sulphafurazole).
536.608.60535	Diarrhea/					Corrective treatment for diarrhea included
	Protocol Defined Diarrhea	4	Severe	Probable	Yes	Kaolectrolyte.
536.609.60604	Rash/					
	Rash on Lower Extremities	5	Mild	Suspected	No	
	Diarrhea/					
536.615.61052	Diarrhea, More Than 3 Watery Stools in 1 Day	4	Severe	Probable	No	
	Contact Dermatitis/					
	Diaper Rash	8	Severe	Probable	No	
536.615.61053	Diarrhea/					
	Diarrhea, More Than 3 Watery Stools in 1 Day	8	Severe	Probable	No	
	Melena/					
	Blood in Stool	8	Moderate	Probable	No	
536.615.61060	Urticaria/					
	Hives	8	Moderate	Probable	Yes	Corrective treatment given for the hives included Benadryl.
536.615.61073	Diarrhea/					
	Severe Diarrhea	4	Severe	Probable	No	
536.621.61512	Vomiting/					
	Vomiting	2	Moderate	Suspected	No	
536.622.61576	Diarrhea/					
	Diarrhea	2	Severe	Probable	No	
536.627.61953	Rash/					
	Rash	2	Mild	Probable	No	
	Abdominal Pain/					
	Abdominal Pain	2	Severe	Probable	No	
536.641.62552	Diarrhea/					
	Loose Stools	2	Severe	Probable	No	
	Vomiting/					
	Vomiting	1	Mild	Probable	No	
536.641.62582	Vomiting/					
	Vomiting Associated to Study Drug Intake	3	Mild	Probable	No	
	Diarrhea/					
536.641.62599	Diarrhea	2	Mild	Probable	Yes	Corrective treatment for the vomiting and diarrhea included saline solution.

536.642.62661	Vomiting/ Vomiting	2	Moderate	Probable	Yes
	Diarrhea/ Diarrhea	3	Moderate	Probable	No

*Day of onset is relative to start of study medication, i.e. day 1 is first day of study medication
Data Source: Appendix D, Listing D.01(b).

APPENDIX III

Patients Included in Protocol-defined Diarrhea(PDD) Analysis: Met Criteria of '3 or more watery stools in a day, 2 watery stools on 2 consecutive days' or Reported an Adverse Event of 'DIARRHEA' On-therapy

PID	PDD	PDDAE	PID	PDD	PDDAE
536.600.59966	Y	Y	536.600.59967	Y	Y
536.600.59968	Y	Y	536.600.59983	Y	Y
536.601.60004	Y		536.601.60008	Y	
536.601.60018	Y		536.601.60021	Y	
536.602.60081	Y		536.602.60085	Y	Y
536.602.60086	Y		536.602.60089	Y	Y
536.603.60154	Y		536.603.60157	Y	
536.606.60382	Y		536.606.60402	Y	Y
536.608.60530	Y		536.608.60535	Y	Y
536.608.60536	Y		536.608.60544	Y	
536.608.60545	Y		536.608.60547	Y	
536.608.60552	Y		536.608.60561	Y	
536.608.60562	Y		536.608.60563	Y	
536.608.60564	Y		536.608.60580	Y	
536.608.60581	Y		536.608.60584	Y	
536.608.60587	Y		536.608.60594	Y	
536.608.60597	Y		536.608.61127	Y	
536.608.61135	Y		536.608.61136	Y	
536.609.60607	Y		536.609.60609	Y	
536.609.60618	Y		536.609.60619	Y	
536.609.60620	Y		536.609.60621	Y	

536.609.60624	Y		536.609.60626	Y	
536.610.60678	Y		536.611.60751	Y	
536.611.60758	Y		536.615.61052	Y	Y
536.615.61053	Y	Y	536.615.61055	Y	
536.615.61058	Y		536.615.61072	Y	
536.615.61073	Y	Y	536.621.61502	Y	
536.621.61504	Y		536.622.61576	Y	Y
536.640.62476	Y		536.640.62485	Y	
536.640.62488	Y		536.641.62558	Y	
536.641.62571	Y		536.641.62589	Y	
536.641.62599	Y	Y	536.642.62644	Y	
536.642.62661	Y	Y			

ADDENDUM TO MEDICAL REVIEW
NDA 50-755, AUGMENTIN ES (90 mg/kg/day ORAL SUSPENSION--14:1 formulation) for Acute Otitis Media due to penicillin resistant *S. pneumoniae*

12/22/2000

Bacteriologic and Clinical Outcome of patients with third tympanocentesis
Eleven patients had a repeat tympanocentesis at the time of failure, beyond the on therapy visit.

PRSP population
Two patients had a baseline pathogen, not *S. pneumoniae,* reisolated from a repeat tap at the time of failure. In the original review, these patients were counted as bacteriologic and clinical failures at the test of cure visit in the FDA penicillin resistant *S. pneumoniae* (PRSP) population.

Patient 600-59904 had *H. influenzae* and *S. pneumoniae* (penicillin MIC= 2μg/mL) isolated from the baseline tympanocentesis; *S. pneumoniae* was isolated from the right ear only. Culture results from the second on therapy tympanocenteses were negative. The patient was declared a clinical failure on d16 and tympanocenteses were repeated. *H. influenzae* but not *S. pneumoniae* was isolated from both ears. Therefore, the patient is a clinical failure but had eradicated the baseline penicillin resistant *S. pneumoniae* by d16.

Patient 600-59910 had *S. pneumoniae* (penicillin MIC= 2μg/mL) isolated from baseline tympanocentesis from both ears and *H. influenzae* isolated from the right ear. The second on therapy tympanocentesis was missed; repeat tympanocentesis was done on d21 in the left ear only, at the time the patient was declared a clinical failure. The right ear exam at this visit was normal. *H. influenzae* but not *S. pneumoniae* was isolated from the d21 tap culture. Therefore, the patient is a clinical failure but eradicated the baseline penicillin resistant *S. pneumoniae* by d21.

Although these patients remained clinical failures at the test of cure assessment for the PRSP population, their bacteriologic outcome for PRSP at the test of cure visit is that of bacteriologic eradication. As a result, the presumed bacteriologic eradication rates in the overall PRSP population at TOC changed from 36.6% to 41.5% in the ITT population and from 41.2% to 47.1% in the per protocol population. Since both patients had PRSP with penicillin MIC= 2μg/mL at baseline, only these results are affected (See table 1).

Table 1 Presumed PRSP bacteriologic outcome at TOC

	Pen MIC≥2μg/mL	Pen MIC=2μg/mL	Pen MIC= 4μg/mL
Population	n/N (%)	n/N (%)	n/N (%)
FDA PP	16/34 (47.1)	11/20 (55.0)	5/14 (35.7)
ITT (missing counted as failures)	17/41 (41.5)	11/23 (47.8)	6/18 (33.3)

PSSP population

Three patients in the PSSP population---600-59930, 600-59949, 608-60536--- also did not have penicillin susceptible *S. pneumoniae* reisolated at the repeat tympanocentesis at the time of failure. These patients would be considered clinical failures but with a bacteriologic outcome of eradication of penicillin susceptible *S. pneumoniae* at the time of failure.

Bilateral Tympanocenteses

Two patients had discordant results for S. pneumoniae at baseline.

Patient 600-59930 and 600-59966 had both PSSP and PRSP isolates at baseline. The study was designed with a unilateral tympanocentesis of the more symptomatic ear, but the investigator at the Israeli site performed bilateral tympanocentesis on patients with bilateral AOM, and consistently counted the results from the left ear; therefore, these 2 patients were not included in the applicant's or the FDA PRSP population for analysis. Patient 600-59930 completed the study and was counted in the PSSP per protocol populations. Patient 600-59966 was withdrawn on d6 for diarrhea and was not included in the clinical or bacteriologic per protocol populations.

/S/

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NDA 50-755
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