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APPLICATION NUMBER:

50-755

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA: 50-755
Drug Name: Augmentin ES Suspension (amoxicillin/clavulanate potassium)
Applicant: SmithKline Beecham Pharmaceuticals
Indication: Acute Otitis Media due to *S. pneumoniae*

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1 Executive Summary

This trial studies the efficacy and safety of Augmentin ES (amoxicillin-clavulanate ratio of 14:1). Regimens with lower doses of amoxicillin (7:1 ratio) have already been approved for the treatment of AOM. As stated in the sponsor's Study Report, the rationale for this increased dosage is to provide efficacy against penicillin resistant cases of *s. pneumoniae*.

This study treated 521 pediatric patients with suspected AOM with Augmentin ES (amoxicillin-clavulanate ratio of 14:1). Based on baseline tympanocentesis, 359 of these patients had a documented baseline pathogen, and 157 of these had streptococcus pneumonia (SP), with or without other pathogens. The SP patients were further classified by penicillin MIC; a total of 41 had values greater than or equal to two (PRSP); 23 had MIC of two and 18 had MIC of four.

Note: The FDA identified a major error in the assessment of per protocol status in data from the original submission dated 4/5/2000. After the sponsor was alerted to this problem, it submitted a revised Study Report (on 9/20/00) and data sets (on 9/22/00), two weeks prior to the action due date. A comprehensive review of the 41 PRSP patients by the statistical and medical officers had found 19 disagreements in PP TOC clinical outcomes between FDA and the original submission. In the revised submission, seven disagreements remained; three of which were deemed unequivocal and the others were based, to some extent, on judgement. On the other hand, the FDA Day 4-6 microbiologic results are nearly identical to those of the sponsor's. However, because of remaining concerns about the TOC clinical results, the outcomes reported in this summary are based on the FDA analysis.

This trial incorporated a repeat tympanocentesis at day 4-6 for all patients with SP, and for some patients without SP. The FDA results were that the Day 4-6 ITT eradication rate was .927¹ (n=41) for the PRSP population. (Two patients had persistent pathogens and one's microbiologic status was "unable to determine"; however, it was also noted that the sponsor changed two PRSP patient's values from "unable to determine" to eradication after FDA received the initial data.) The corresponding rate for the FDA's bacteriologic per protocol (PP) group among PRSP patients was .939 (n=33). Similar FDA results were seen for the overall SP population (.943 for ITT and .984 for PP). In addition, of the patients with pathogens other than SP, a great majority of the repeat tympanocenteses showed eradication. Sponsor results for these 4-6 day microbiologic results were the same. Of course, it is also important to consider the confidence intervals for these important estimates; for example, the 95% confidence interval for the FDA's ITT PRSP Day 4-6 bacteriologic eradication estimate is (.801, .985), and the corresponding interval for the FDA's PP PRSP estimate is (.798, .993).

The key issue of concern in the study results is the clinical outcome at TOC data, especially among PRSP patients. The sponsor's original per protocol populations, especially their PP clinical population exclude many patients simply because they went on other antibiotic therapy for AOM. From the FDA perspective, these patients are failures and belong in the PP populations, unless they have other protocol violations. As discussed above, after queries from the FDA, the sponsor recognized that an error in their analysis which had a major effect on the PP estimate of TOC clinical success had been made, and resubmitted a new analysis just prior to the end of the review period. Thus, while the FDA's results differ substantially from the original sponsor results, they are somewhat closer to those of the re-analysis. FDA estimates of TOC clinical success in the PRSP populations were .366 and .424 for the ITT and PP populations, respectively (n=41 and 33), the corresponding confidence intervals are (.221, .531) and (.255, .608). The sponsor's revised estimate of PP TOC clinical success is .60 with n=30. However, the FDA's most generous assessment of PP

¹ All ITT results presented in this summary are based on counting missing values as failures.

clinical TOC success is .55, in which the four patients who were judged to be failures by the FDA Medical Officer are considered successes as indicated by the sponsor. The corresponding ITT results are somewhat lower. In any case, these relatively low rates of TOC clinical success strongly calls into question the appropriate interpretation of the much higher bacteriologic eradication rates seen at 4-6 days.

It is critical to compare these relatively low success rates for clinical TOC in PRSP to what would be expected had no therapy been given. However, the sponsor has not provided data to address this, and the only relevant data known to this reviewer does not provide support for efficacy (this issue is addressed in Section 8.2). Furthermore, since these data are neither drawn from a random sample nor have a randomized comparative group, any conclusions should be made very cautiously.

A summary of the important observations and comments:

- The estimates of pathogen eradication rates are greater than 90% for all groups of interest; however lower bounds of confidence interval for PRSP are about 80%.
- The FDA's estimates of clinical success rates at TOC, especially for PRSP, are dramatically lower than the pathogen eradication rates at Days 4-6. This result strongly calls into question whether full eradication had really occurred.
- The clinical efficacy rates for PRSP patients fall below the threshold that is expected for effective AOM therapy. Demonstration of efficacy among PRSP patients requires knowledge of how this same group of patients would have fared without treatment. However, no pertinent data about the natural history of PRSP was provided in the submission. Furthermore, the only relevant published data, known to this reviewer, do not support a conclusion of clinical efficacy. In addition, this study is not a random sample and is of small size, and thus conclusions should be drawn carefully.
- The other stated primary objective of this trial was to consider efficacy in amoxicillin/clavulanic acid resistance cases. The FDA results for PP TOC clinical response were .435 for amoxicillin MIC=2 (n=23), .750 for amoxicillin MIC=4 (n=4), and .000 for amoxicillin MIC=8 (n=4).

In summary, the study data do not provide evidence that this new drug has sustained efficacy against PRSP once it is withdrawn, despite the high level of eradication observed at Days 4-6. This application provides no basis for concluding clinical efficacy, as the TOC success rates fall considerably below what is typically expected for AOM therapy, and because there is no information about the natural untreated cure rate of the PRSP population provided in this submission as a means of comparison. It is noted that the point estimates of success for other pathogen categories studied appears to be similar to those found in some products that have been approved for AOM. However, there is no demonstrated advantage of this Augmentin 14:1 regimen over the lower dose Augmentin 7:1 regimen.

2 Introduction

Augmentin ES is an oral antibiotic combination of amoxicillin and clavulanic acid with a 14:1 ratio of amoxicillin to clavulanate potassium. The sponsor states in the introduction of the Study Report "This formulation is intended to treat AOM in cases where DRSP is suspected", where AOM denotes acute otitis media and DRSP denotes drug-resistant-streptococcus-pneumoniae. Since AOM is typically treated empirically, the sponsor also intends to show that Augmentin ES provides coverage for a broad spectrum of AOM pathogens.

This study incorporated a repeat tympanocentesis design so that pathogen eradication could be directly assessed after 4-6 days on drug. Determination of efficacy in a single arm trial involves a comparison of the obtained results and corresponding confidence intervals with expected rates

obtained with no therapy, and perhaps with other therapy; however this was not directly addressed by the sponsor.

2.1 Study Objectives

The stated study goals focused on demonstration of efficacy in the drug resistant subgroups, but secondarily considered efficacy and safety overall.

The sponsor states in Volume 5 of the Study Report:

The primary objective of this study was two-fold:

- To obtain bacteriological efficacy data for *Augmentin* ES in the treatment of children with AOM due to *S. pneumoniae* with penicillin MICs of \geq 2.0 mcg/mL (per 9 December 1999 amendment to the protocol).
- 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 were:

- 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 \geq 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.

During the protocol review process, the FDA MO emphasized its perspective that the clinical TOC endpoint was the major outcome variable; however, the sponsor chose not to revise its protocol in accordance with this advice.

2.2 Study Design

This trial studied focused on microbiologic outcome, baseline pathogens were assessed by tympanocentesis (or via a ruptured membrane) in all patients. All patients with baseline streptococcus pneumoniae (SP), along with some others had a repeat tympanocentesis at 4-6 days. Global assessment of clinical outcome at test of cure (TOC) was made at 25-28 days.

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The sponsor provides the following synopsis of the study design in the Study Report:

This was an open-label, non-comparative, multi-center study of children presenting with protocol-defined AOM. Patients who met eligibility criteria, received 10 days of *Augmentin* ES 90/6.4 mg/kg/day in divided doses q12h. All patients who received study medication had a tympanocentesis procedure performed within the 24 hours before study entry in order to obtain specimens of MEF for bacteriological evaluation. If the patient presented with a ruptured TM, the culture specimen was obtained directly, provided the rupture was of <24 hours duration. Patients from whom *S. pneumoniae* (alone or in combination with other pathogens) was isolated had a repeat tympanocentesis 4 to 6 days after start of therapy. Patients from whom other pathogens only were isolated had a repeat tympanocentesis either in instances of clinical failure, or alternatively, a few centers performed repeat tympanocentesis at day 4-6 on all patients who had bacterial growth on initial tympanocentesis. Patients were monitored with an on-therapy visit (day 4-6), returned for an end-of-treatment visit (day 12-15), and a test-of-cure visit (day 25-28).

3 Statistical Methods

3.1 Sponsor's Statistical Plan

Originally a target sample size of 700 patients was planned to yield 14 isolates of amoxicillin/clavulanic acid MICs ≥ 4 . The protocol was later amended to add an objective to study patients with PRSP (*S. pneumoniae* with penicillin MIC of ≥ 2), requiring 450 patients to yield approximately 20 patients for the PRSP analysis. In November 1999, 529 patients had been enrolled, with a sufficient number for analysis of PRSP; these data were submitted in the Study Report. Since the study is ongoing with the goal of collecting more information about *S. pneumoniae* patients with amoxicillin/clavulanic acid MICs ≥ 4 (ACRSP), the sponsor has stated that the submitted results regarding such patients are "interim".

The planned primary efficacy variable was bacteriological response at the on-therapy visit (day 4-6) in PRSP and in amoxicillin/clavulanic acid resistant SP patients. Secondary efficacy variables included bacteriological response for other pathogens, clinical efficacy response at end of treatment, and clinical efficacy response at test of cure (TOC).

As stated in the Study Report, inclusion in any PP population required:

- Patient must have 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. Non-compliance with the study medication schedule prior to withdrawal from or completion of the study is considered a protocol violation.
- Patient must not have received any prohibited medication as defined in the protocol.
- Patient must have received at least three full days of study medication

In addition, to be included in the Bacteriological PP, the patient had to have a positive baseline culture. SP patients also had to have a culture taken at days 4-6. To be included in Clinical PP, the patient also needed assessment at baseline and at the relevant clinical assessment time (e.g., TOC for the TOC Clinical PP).

3.2 Statistical Reviewer's Comments on Sponsor's Statistical Plan

- The protocol did not mention confidence intervals, nor did it specify a standard that the estimate had to meet. In addition, there was no discussion about expected rate of spontaneous resolution in this population.
- At times, the protocol suggested the PP analyses are primary, but this is not clearly addressed.
- The protocol was somewhat unclear about exact amoxicillin/clavulanic acid MIC of interest. Often it focused on amoxicillin/clavulanic acid MIC=4, but sometimes MIC>4.
- FDA analyses consider confidence intervals, both ITT and PP analyses, and ACMIC values greater than 4.

4 Baseline Profile

As this is not a comparative trial, it is critical to describe the population as precisely as possible, and to describe the major subgroups as well. A detailed tabulation of baseline characteristics for several important populations is presented below in Table 1. It is interesting to note that, in comparison to the overall and the SP population, the PRSP patients have numerically higher rates of multiple pathogens, antibiotic use in the previous three months, and young age. A tabulation of a mutually exclusive categorization of pathogen, an ad hoc classification devised by the statistical reviewer is presented in Table 2.

Table 1: Baseline proportions of selected attributes by population

Attribute	ITT: No Baseline Pathogen		ITT: Baseline Pathogen		ITT:SP		ITT:PRSP		FDA Clinical PP: PRSP	
	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N
S. Pneumo documented	0.000	162	0.437	359	1.000	157	1.000	41	1.000	33
PRSP documented	0.000	162	0.114	359	0.261	157	1.000	41	1.000	33
>1 pathogen documented	0.000	162	0.139	359	0.280	157	0.390	41	0.485	33
Purulence	.	0	0.072	359	0.089	157	0.122	41	0.152	33
Abnormal mobility	.	0	0.980	343	0.987	149	0.949	39	0.935	31
Abnormal color	.	0	0.989	355	0.993	153	0.974	39	0.968	31
Abnormal opacity	.	0	0.983	354	0.980	153	0.949	39	0.935	31
Otalgia	.	0	0.848	355	0.840	156	0.805	41	0.788	33
Redness	.	0	0.868	355	0.863	153	0.846	39	0.806	31
Abnormal position	.	0	0.943	351	0.928	152	0.923	39	0.903	31
USA center	0.562	162	0.526	359	0.484	157	0.537	41	0.576	33
Antibiotics previous three months	0.449	147	0.530	285	0.521	121	0.808	26	0.773	22
Day care	0.340	147	0.404	285	0.405	121	0.462	26	0.409	22
Age >18 months	0.469	162	0.354	359	0.357	157	0.220	41	0.242	33
Temperature >98.6	.	0	0.666	338	0.730	152	0.675	40	0.719	32
Male sex	0.611	162	0.593	359	0.561	157	0.561	41	0.515	33

Table 2: Number of patients falling in each mutually exclusive pathogen category

Mutually exclusive pathogen category*	Number
No pathogen	162
Multiple pathogens but no SP	6
S aureus only	9
Moraxella only	17
S pyogenes only	15
H influenzae only	155
SP (MIC <2), plus other pathogen	28
SP (MIC=2), plus other pathogen	10
SP (MIC=4), plus other pathogen	6
SP alone (MIC unknown)	7
SP alone (MIC <2)	81
SP alone (MIC=2)	13
SP alone (MIC=4)	12
TOTAL	521

* This classification is devised by the statistical reviewer

5 Study Disposition

There were 843 patients screened for this trial, of which 529 were eligible, and 521 received at least one dose of study drug. The sponsor's assessment of the disposition of the ITT patients is shown in Table 3.

Table 3: Sponsor specification of study disposition of 521 ITT patients

	N=521	
	n	(%)
Completed the Study	305	(58.5)
Reasons for 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	(1.3)
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 of Study Report

Membership in key analysis subgroups is summarized in Table 4.

Table 4: Membership in key analysis subgroups by important pathogen categories - uses revised sponsor data

	N in ITT	N in Sponsor Bact SP PP	N in Sponsor Clinical PP	N in FDA Bact SP PP	N in FDA Clinical PP
All	521	--	289	--	295
Pathogen Present	359	--	289	--	295
SP Present	157	123	131	123	135
PRSP Present	41	33	30	33	33

6 Efficacy Results

The sponsor's stated primary purpose of this study is to consider the bacteriologic response at the on-therapy culture at 4-6 days; however, the assessment of the clinical outcome at the test of cure (TOC) visit is critical to the interpretation of this early culture result.

6.1 Data quality

A major flaw in the definition of PP membership was identified by the FDA, which had a substantial impact on the clinical TOC PP results. In September 2000, the sponsor submitted revised study tables and data sets in response to notification about this critical error. Since the FDA has done a comprehensive review of all PRSP patients, it was able to determine that the revised data had corrected much of the problem, but not all of it. Three of the 41 PRSP patients still were inappropriately excluded from the TOC clinical PP.

However, several more patients beyond the PRSP data set were identified whose termination codes were "insufficient therapeutic effect" who were inappropriately excluded from the sponsor PP and/or not considered to be failures. There was not sufficient time to correct the FDA data set with respect to these problems and any other enduring problems. Thus, because of remaining problems the sponsor's data set, it is likely that the estimates contained in this report relevant to patients outside the PRSP population are slightly inaccurate.

The sponsor explains the source of the original error as the failure to do a "manual analysis" that is used to determine the appropriateness of the classification of protocol violator. Apparently, even this new manual analysis did not capture all misclassifications.

6.2 Primary FDA efficacy results

With respect to revised data submitted in September 2000, the FDA modified the TOC clinical assessment and/or PP membership of a small number of patients. If patients still met the protocol definition of AOM at TOC, the FDA considered them clinical failures. All patients who were put on antibiotics because of AOM by TOC were considered clinical failures. Additional modifications to the assessments were the results of a review by the FDA Medical Officer (MO), who examined individual CRFs for all PRSP patients and a subset of other patients. The FDA also reconsidered assignment of the PP populations. The sponsor's original analysis had excluded numerous patients who went on additional antibiotic therapy for AOM, because they were deemed to have "prohibited" medications or because outcomes were not assessed at pre-specified visits. However, if no other protocol violations were observed, the FDA included such patients in the PP analyses as failures, except in a few cases where a switch in antibiotic was apparently due to adverse events. The great majority of these discrepancies that occurred in the PP clinical outcomes were resolved in the revised sponsor data, as shown in Table 5. However, some discrepancies remain, it is further noted that PRSP patients had a disproportionately high rate of these discrepancies. Furthermore, it is likely that there are other discrepancies that are yet to be identified.

Table 5: Correspondence of FDA and Sponsor PP TOC Clinical outcomes (uses revised sponsor data)

Status	PP TOC Clinical Outcome		Number		
	Sponsor	FDA	Baseline Pathogen	SP	PRSP
No disagreement in PP Clinical Outcome	Excluded	Excluded	64	22	8
	Failure	Failure	80	32	12
	Success	Success	202	93	14
New antibiotic given for AOM by TOC because of clinical failure	Excluded	Failure	5	3	2
Protocol defined AOM criteria still met at TOC	Success	Failure	5	4	2
Prohibited drug given after failure	Excluded	Failure	1	1	1
On therapy visit failure (per FDA MO)	Success	Failure	2	2	2

The primary efficacy outcomes by the FDA analysis are presented in Table 6. It is seen that PRSP TOC clinical success rates are roughly about .35 or .40, depending on the specific analysis, with the lower bound of the corresponding confidence intervals around .20 to .25. The difference in TOC clinical outcomes between PRSP and PSSP is highly statistically significant.

Table 6: Major efficacy outcomes by FDA and corresponding exact 95% confidence intervals (Micro refers to microbiologic outcome at Day 4-6, Clinical refers to clinical outcome at TOC, and Both refers to a combination of the two) (uses revised sponsor data set)

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
<i>S. Pneumoniae</i>	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
	Both	157	0.611	0.530	0.688	117	0.701	0.609	0.782
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
	Both	109	0.706	0.611	0.790	82	0.793	0.689	0.874
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
	Both	41	0.341	0.201	0.506	29	0.414	0.235	0.611
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
	Both	23	0.391	0.197	0.615	18	0.444	0.215	0.692
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
	Both	18	0.278	0.097	0.535	11	0.364	0.109	0.692

6.3 Detailed results in PRSP population

Table 7 focuses on the critical variable, clinical TOC outcome, as assessed by the FDA. This table starts with the ITT population and gradually winnows the data down to the FDA PP population. Results are relatively stable regardless of which analysis set used, suggesting a robustness of these findings. Table 8 considers other estimates that are based, at least in part, on the sponsor outcomes. There are seven patients whose TOC clinical PP outcomes are different between FDA and the sponsor as indicated in Table 5. Three of these cases are patients excluded from the sponsor's clinical TOC PP population; however, the FDA's view is that these are unequivocal members of the clinical TOC PP population. The remaining four patients are ones that the FDA MO judged to be failures, after being considered successes by the sponsors. While the FDA perspective is that the sponsor's misclassification is quite clear-cut, a sensitivity analysis provides the results when these patients are analyzed as success (hence the "optimistic" outcome in Table 8). Thus, these two tables provide a range of estimates for the clinical TOC success rate. The range of reasonable FDA estimates varies from .366 to .545; however, the .545 estimate is almost certainly too optimistic.

Table 7: FDA clinical TOC results for PRSP in increasingly select 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 with late positive culture as a failure **	34	.412	20	.450	14	.357
FDA PP	33	.424	20	.450	13	.385

*Specifically: to create this population patients with no other violations who were put on new antibiotic for AOM because of AE are added to the FDA PP

**PID=536.600.59953. This patient was excluded from the FDA PP in the main tables in this review. However, given information provided in the last week of the review period, he probably should have been classified as a clinical TOC PP failure.

Table 8: Additional clinical TOC PP results with "optimistic" outcomes: four patients who were judged to be successes by the sponsor but failures by the FDA MO, are counted as successes in this table

Population	PRSP		PRSP (MIC=2)		PRSP (MIC=4)	
	N	Success Rate	N	Success Rate	N	Success Rate
FDA PP plus* with optimistic outcomes	34	.529	20	.550	14	.500
FDA PP with optimistic outcomes	33	.545	20	.550	13	.538
Sponsor PP and optimistic outcomes	30	.600	19	.579	11	.636

* PID=536.600.59953. This patient was excluded from the FDA PP in the main tables in this review. However, given information provided in the last week of the review period, he probably should have been classified as a clinical TOC PP failure

Table 9 provides comprehensive information about the FDA results for the PRSP population.

Table 9: Comprehensive tabulation of FDA outcomes for PRSP population: PPB denotes Bacteriologic PP and PPC denotes Clinical TOC PP

FDA Micro: Day 4-6	FDA TOC Clinical Outcome	Excluded from FDA PPB or FDA PPC?	PRSP	PRSP (MIC=2)	PRSP (MIC=4)
Success	Success	No	12	8	4
		PPB: insufficient drug	1	1	
		Both: prohibited drug	1		1
Success	Missing	PPC: adverse event	1	1	
		PPC: missing	1		1
Success	Missing, but later culture positive**	PPC: missing	1		1
Success	Failure	No	14	9	5
		PPC or both: adverse event	3	1	2
		PPB: insufficient drug	3	1	2
Success? *	Failure	No	1	1	
Failure	Success	No	1		1
Failure	Failure	No	1		1
Missing	Missing	Both: missing	1	1	
TOTAL			41	23	18

* Primary ear was culture negative at Day 4-6, but secondary ear was positive at Day 4-6. However, MIC=2 at baseline and MIC=1 at Day 4-6 (PID=536.600.59986)

** Culture taken after Day 4-6 was positive for PRSP on Day 13 and then dropped out (PID=536.600.59953)

6.4 PRSP results by other pathogen status

When PRSP patients are stratified by MIC and presence of other pathogens, the success rates are numerically higher among patients with multiple infections, as seen in Table 10. This observation is particularly striking with the FDA analysis; in fact the association was statistically significant ($p < 0.05$ for both ITT and PP populations). No apparent explanation for this finding could be found among covariates in the data. Since this analysis was not pre-specified, it should be interpreted cautiously.

Table 10: TOC clinical success rates for PRSP patients stratified by MIC and presence of other baseline pathogen (uses revised sponsor data)

Baseline Pathogen Profile	ITT (missing counted as failures)				PP			
	Sponsor		FDA		Sponsor		FDA	
	N	Success Rate	N	Success Rate	N	Success Rate	N	Success Rate
PRSP (MIC=2) with other pathogen	10	.600	10	.600	10	.600	10	.600
PRSP (MIC=4) with other pathogen	6	.667	6	.667	5	.800	6	.667
PRSP alone (MIC=2)	13	.385	13	.231	9	.556	11	.273
PRSP alone (MIC=4)	12	.333	12	.167	6	.500	9	.111

6.5 Comprehensive efficacy results by both Sponsor and FDA

The clinical success rates for some important populations are exhibited in Table 11 and the corresponding Day 4-6 microbiological results are seen in Table 12.

Table 11: TOC Clinical success rates for different populations and definitions (failures are counted as missing for ITT) - (uses revised sponsor data)

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
<i>S. pneumoniae</i>	157	0.675	157	0.637	131	0.756	135	0.689
<i>S. pneumoniae</i> Penicillin MIC <2	109	0.752	109	0.734	94	0.809	95	0.779
<i>S. pneumoniae</i> Penicillin MIC=2	23	0.478	23	0.391	19	0.579	20	0.450
<i>S. pneumoniae</i> Penicillin MIC=4	18	0.444	18	0.333	11	0.636	13	0.385
<i>S. pneumoniae</i> Penicillin MIC >=2	41	0.463	41	0.366	30	0.600	33	0.424
<i>S. pneumoniae</i> Amox MIC <2	119	0.739	119	0.723	103	0.796	104	0.769
<i>S. pneumoniae</i> Amox MIC=2	28	0.500	28	0.393	22	0.591	23	0.435
<i>S. pneumoniae</i> Amox MIC=4	4	0.750	4	0.750	4	0.750	4	0.750
<i>S. pneumoniae</i> Amox MIC=8	6	0.167	6	0.000	2	0.500	4	0.000
<i>H. influenzae</i>	197	0.594	197	0.594	154	0.688	156	0.679
<i>M. catarrhalis</i>	29	0.483	29	0.483	25	0.560	25	0.560
<i>S. pyogenes</i>	16	0.813	16	0.750	14	0.857	14	0.786
<i>S. aureus</i>	12	0.667	12	0.667	11	0.727	12	0.667

Note: Corresponding PP populations are used; for example, the Sponsor's PP population is used for its rates, and so forth.

Note2: The sponsor presented results by amoxicillin/clavulanate MIC values; however, only amoxicillin MIC values were available for FDA analysis. Differences between the two were minimal.

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Table 12: Day 4-6 bacteriologic success rates for different populations and definitions (failures are counted as missing for ITT) - (uses revised sponsor data)

Population	ITT (Missing count as failures)				PP			
	Sponsor		FDA		Sponsor		FDA	
	N	Rate	N	Rate	N	Rate	N	Rate
<i>S. pneumoniae</i>	157	0.943	157	0.943	123	0.984	123	0.984
<i>S. pneumoniae</i> Penicillin MIC <2	109	0.945	109	0.945	84	1.000	84	1.000
<i>S. pneumoniae</i> Penicillin MIC=2	23	0.957	23	0.957	19	1.000	19	1.000
<i>S. pneumoniae</i> Penicillin MIC=4	18	0.889	18	0.889	14	0.857	14	0.857
<i>S. pneumoniae</i> Penicillin MIC ≥ 2	41	0.927	41	0.927	33	0.939	33	0.939
<i>S. pneumoniae</i> Amox MIC <2	119	0.950	119	0.950	93	1.000	93	1.000
<i>S. pneumoniae</i> Amox MIC=2	28	0.929	28	0.929	22	0.955	22	0.955
<i>S. pneumoniae</i> Amox MIC=4	4	1.000	4	1.000	4	1.000	4	1.000
<i>S. pneumoniae</i> Amox MIC=8	6	0.833	6	0.833	4	0.750	4	0.750

Note: Corresponding PP populations are used; that is, the Sponsor's PP population is used for its rates, and so forth.

A summary of the sponsor's PP bacteriologic results by pathogen other than SP compiled by the sponsor is presented in Table 13.

Table 13: Sponsor's summary of Day 4-6 PP bacteriologic results by pathogens other than SP (Uses revised Sponsor data)

Pathogen	Success		Failure	
	n/N	(%)	n/N	(%)
<i>Known Response*</i>				
<i>H. influenzae</i>	75/81	(93.8)	5/81	(6.2)
<i>M. catarrhalis</i>	12/12	(100.0)	0	
<i>S. aureus</i>	1/2	(50.0)	1/2	(50.0)

Source: Table 19 of Revised Study Report

6.6 End of treatment clinical outcome

In the September 2000 submission, the sponsor argues for the importance of the end of treatment (EOT) clinical outcome results for which the success rates are substantially higher than at TOC (see Table 14). However the FDA has traditionally assessed therapies by outcome at the TOC visit. In fact, all the data observed for PRSP patients in this study are consistent with the possibility that PRSP is suppressed during the therapy period, but that it reemerges when therapy is withdrawn.

Furthermore, it is important to note that the last patient included in this submission was seen in November 1999, but the protocol amendment that switched the primary clinical variable from TOC to EOT was submitted in December 1999. The timing of this amendment is of concern.

A brief summary of clinical results at EOT is provided in Table 14.

Table 14: EOT clinical success rate for PRSP patients (uses revised sponsor data)

ITT (Missing count as failures)				PP			
Sponsor		FDA		Sponsor		FDA	
N	Rate	N	Rate	N	Rate	N	Rate
41	.707	41	.659	32	.875	34	.765

7 Safety

A series of tables excerpted from the sponsor's Study Report provide a summary regarding the adverse event (AE) profile. These tables indicate that mean study duration was more than nine days. About 37% of patients had at least one reported AE, with vomiting the most common at about 7%. The percentage of patients with a probable/suspected drug related AE was 12.5%, primarily with skin or gastrointestinal system complaints. Nearly 18% experienced a moderate AE and 4% experience a severe AE. About 5% of the patients were withdrawn due to their AE, primarily due to gastrointestinal events. And, finally, 12.5% of the children experienced protocol-defined diarrhea.

Table 15: Duration of study medication (Sponsor table)

Duration of Study Medication Number of Days, n (%)	Augmentin ES	
	N=521	
< 5	34	(6.5)
5 - 10	395	(75.8)
> 10	71	(13.6)
Unknown	21	(4.0)
Duration of Days	N=500	
Mean (SD)	9.37 (2.03)	
Median	10	
Min, Max	0.5, 11	

Source: Sponsor Study Report Table 28

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Table 16: Most frequent adverse events (Sponsor table)

Adverse Experience by Preferred Term	Augmentin ES	
	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	13	(2.5)
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)

Source: Sponsor Study Report Table 29

Table 17: Adverse events with probable/suspected relation to study medication (Sponsor table)

Adverse Experience by Preferred Term	Augmentin ES	
	n	(%)
Patients With At Least One AE of Probable or Suspected Relationship	65	(12.5)
Contact Dermatitis	20	(3.8)
Diarrhea	16	(3.1)
Vomiting	13	(2.5)
Rash	7	(1.3)

Source: Sponsor study report: Table 30

Table 18: Adverse event rates by severity (Sponsor table)

Severity of AE	Augmentin ES	
	n	(%)
Patients Reporting At Least One AE	193	(37.0)
Mild	83	(15.9)
Moderate	90	(17.3)
Severe	20	(3.8)

Source: Sponsor study report: Table 31

Table 19: Adverse events leading to withdrawal by body system (Sponsor table)

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)

Source: Sponsor Study Report: Table 33

Table 20: Patients with Protocol Defined Diarrhea (Sponsor table)

	n	(%)
Patients with PDD		
Yes	65	(12.5)
No	456	(87.5)

Source: Sponsor Study Report: Table 35

8 Conclusions and Comments

8.1 Summary of study findings

The following summarizes the findings of the FDA efficacy analysis. Sponsor results were very similar except for PRSP PP clinical TOC estimates.

- 521 patients were treated with the study drug, of these 359 had a positive culture at baseline, of these 157 had SP at baseline, of these 41 has PRSP, and of these 18 had PRSP MIC=4.
- At baseline, the PRSP patients had a relatively high rate of previous antibiotic use and multiple pathogens. There were relatively few patients older than 18 months.
- Approximately 80% of the PRSP patients were retained in the FDA clinical PP population.
- Microbiologic success at Day 4-6 was observed in over 90% of PSSP patients, and likewise for PRSP patients. However, the rate among the PRSP (MIC=4) subset was slightly lower.
- FDA Clinical TOC success rates for the SP population was about .64 for the ITT population and .69 for the PP population.
- FDA Clinical TOC success rates for the PRSP population was about .37 (ITT) and .42 (PP).
- The point estimates for FDA Clinical TOC rates decline with penicillin MIC; for example, the ITT rates for ≤ 2 , 2, and 4 are .73, .39, and .33 respectively. This decline is statistically significant.
- There were few patients with amoxicillin resistance of 4 or greater; however, substantially poorer clinical results are seen with amoxicillin MIC=2 than with MIC ≤ 2 .

- The overall clinical TOC success rate for all patients with baseline pathogens was about .61 (ITT) and .69 (PP).
- The two largest other pathogen categories are H. influenzae and M. catarrhalis; the respective FDA Clinical TOC PP rates are about .68 and .56. However, it should be noted that a number of these had other pathogens including PRSP.

8.2 Comments on PRSP results

Without reliable information about the natural spontaneous recovery rate in PRSP, it is very difficult to interpret these data. Furthermore, the protocol does not pre-specify a threshold that the observed rate needed to meet. While not directly relevant to the demonstration of efficacy, the analysis demonstrates that the PRSP clinical success rates are much lower than those observed in the penicillin susceptible SP population and that this difference is highly statistically significant. Furthermore, these point estimates are lower than the rates generally seen with effective AOM therapy. Based on the information available, it is not possible to conclude that the study regimen has any efficacy against PRSP. It should be pointed out that this does not necessarily mean that the regimen has no efficacy, but rather that without clear-cut data about the untreated rate in PRSP, there is no basis for establishing this efficacy.

It is well recognized that spontaneous recovery from bacterial AOM is expected in a non-trivial fraction of the population. Marchant et al. ("Measuring the comparative efficacy of antibacterial agents for acute otitis media: the Pollyanna phenomenon", *Journal of Pediatrics*, January 1992) estimates that the clinical efficacy rate in patients with bacterial AOM treated with a drug with no antibacterial effect would be .71. This estimate is based on data that show .27 of bacterial AOM patients will achieve bacterial eradication spontaneously, and additional data that show clinical success of .933 for eradicated patients and .625 for patients without eradication. These conditional probabilities can be used to estimate the unconditional probability of clinical success:

$$\begin{aligned} P(\text{clinical success}) = & \\ & P(\text{eradication}) * P(\text{clinical success given eradication}) + \\ & P(\text{non eradication}) * P(\text{clinical success given non eradication}). \end{aligned}$$

Thus, for a drug with no therapeutic benefit, Marchant et al. estimate for the expected clinical success rate is computed as $.71 = (.27)(.933) + (1-.27)(.625)$. It should be understood that this estimate is based on all bacterial AOM and is not specific to PRSP, and the corresponding rates for this subset of bacterial AOM could be somewhat different. Furthermore, their estimates refer to clinical success after 3-6 days of therapy. Nevertheless, their main point is relevant to the current study's clinical TOC results; that is, a drug with zero efficacy is likely to yield a clinical estimate that is considerably greater than zero in patients with bacterial AOM. Marchant et al. strongly recommend using information from a second tympanocentesis to better discriminate between therapies. However, the poor clinical results seen at TOC in the current study, suggest that a second tympanocentesis at TOC would be much more informative than the one actually taken at Day 4-6, particularly for patients with resistant pathogens. It should be noted that the early bacteriologic success seen in the current study was far higher than the untreated estimate of .27, thus providing support to the conclusion that at this time point, the drug was having an impact. Furthermore, the Marchant et al. estimate of .71 for clinical success in untreated bacterial AOM was based on a Day 3-6 clinical assessment and the corresponding rate at TOC would almost certainly be lower. Nevertheless, based on the available information, it would be very difficult to defend the position that the relatively low clinical success rates observed at TOC in this study are almost certainly better

than what would be achieved by placebo. Furthermore, this TOC clinical result strongly diminishes the importance of the on therapy finding.

It is often noted that PRSP patients are disproportionately represented among treatment failures in the literature. In fact, it is certainly not surprising that PRSP patients fare less well than PSSP patients on penicillin type therapy. However, such an observation does not shed light on a) whether or not PRSP patients are less likely to resolve spontaneously than PSSP patients when no treatment is given or b) whether PRSP patients have an especially low rate of spontaneous recovery.

The above discussion and the findings of this particular study certainly argue for assessment of microbiological eradication to be made at a time that is concurrent with the clinical TOC or failure date. Interestingly, in the PRSP population, absolutely no relationship was observed between early microbiologic outcome and the FDA clinical TOC outcome. Two of the 33 PRSP clinical PP patients had microbiologic persistence at Days 4-6, of these one was a failure and one a TOC clinical success by the FDA analysis. Furthermore, 31 of the PRSP clinical PP population were observed to be microbiologically eradicated at Days 4-6, of these 18 ultimately were failures and 13 were TOC clinical successes.

See the Executive Summary for a discussion of the major results.

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