CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-785

STATISTICAL REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION (NDA):	NDA 50-785
NAME OF DRUG:	Augmentin XR™ (amoxicillin/clavulanate 16:1)
INDICATION(S):	Community-Acquired Pneumonia, Acute Bacterial Sinusitis
APPLICANT:	GlaxoSmithKline
SUBMISSION DATE:	March 29, 2002
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1. EXECUTIVE SUMMARY

This NDA was submitted originally for the indications: Acute Bacterial Sinusitis (ABS), Community-Acquired Pneumonia (CAP) due to susceptible strains of common pathogens, including beta-lactamase producing strains of H. *influenzae* and M. *catarrhalis*. In the previous submission, the claim for ABS due to PRSP was not considered by the division because of a divisional policy which requires that efficacy for the treatment of PRSP be demonstrated in CAP prior to other respiratory indications. The review was completed and an Action Letter of December 12, 2001 indicated that this product was not approvable.

The sponsor re-submitted Integrated Summary of Efficacy (ISE) of the clinical program that supports the efficacy of Augmentin XR as an antibacterial agent for use in the respiratory tract infections of CAP and ABS. However, the focus of this review will be mainly on the efficacy of patients with CAP and ABS due to PRSP.

I. Community Acquired Pneumonia

There were three Principal controlled studies (studies 546, 556 and 557) and one uncontrolled study 547 submitted for CAP indication.

In Study 546, a 7 day course of Augmentin XR was compared with amoxicillin/ clavulanate 875/125mg (7:1) bid for 7 days, which is the conventional Augmentin formulation currently used in the US for the treatment of CAP. In study 557, Augmentin XR was compared with Augmentin 875/125mg (7:1) tid, which is the approved Augmentin dosage regimen for CAP in Spain and Italy but not in US. In Study 556, Augmentin XR was compared with Augmentin 1000/125mg (8:1) tid, which is the approved Augmentin dosage regimen for CAP in France.

The principal conclusions of the overall efficacy assessment of Augmentin XR in CAP were based on the clinical and microbiological cure rates at the Test of Cure Visit.

In study 546, in the Clinical PP population at test of cure visit, the clinical success rates were; (86.3% in the Augmentin XR group and 91.2% in the Augmentin 875/125mg group). In the ITT population, the clinical success rate at test of cure was 78.0% for Augmentin XR and 82.6% for Augmentin 875/125mg. In both populations(95% CIs: -11.0, 1.2 for the Clinical PP analysis and -11.4, 2.3 for the ITT analysis) Augmentin XR failed to demonstrate non-inferiority to Augmentin 875/125 (Table 5), using a non-inferiority margin of 10%.

The bacteriological success rates in study 546 for the Bacteriology PP population were 78.1% in the Augmentin XR group and 84.6% in the Augmentin 875/125mg group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were

69.2% in the Augmentin XR group and 83.3% in the Augmentin 875/125mg group. The 95% confidence limits for all the studies are given in Table 5 for reference.

In Study 556, the clinical success rate at test of cure for the Clinical PP population was 91.5% for Augmentin XR and 93.0% for Augmentin 1000/125mg. Results in the ITT population were 81.1% and 85.7% in the respective treatment groups. The clinical response in the PP population for Augmentin XR 2000/125mg bid was concluded to be as good as Augmentin 1000/125mg tid (95% CI: -8.3, 5.4). In the ITT population, Augmentin XR 2000/125mg failed to demonstrate non-inferiority (95% CI: -12.5, 3.2), using a non-inferiority margin of 10%.

In Study 556, the bacteriological success rates at test of cure for the Bacteriology PP population were 90.6% in the Augmentin XR group and 84.4% in the Augmentin 1000/125mg group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 84.1% in the Augmentin XR group and 76.6% in the Augmentin 1000/125mg group.

In Study 557, the clinical success rate in the Clinical PP test of cure population was 94.7% in the Augmentin XR group and 88.8% in the Augmentin 875/125mg group. Results in the ITT population were 84.8% and 77.0% in the respective treatment groups. In each population, the clinical efficacy of Augmentin XR was concluded to be at least as good as that of Augmentin 875/125mg, based on using a non-inferiority margin of 10% (95% CI: -1.1, 13.0 for Clinical PP and -0.8, 16.4 for the ITT analyses).

The bacteriological success rates at test of cure for the Bacteriology PP population in Study 557 were 85.0% in the Augmentin XR group and 77.3% in the Augmentin 875/125mg group. In the Bacteriology ITT population the bacteriological success rates were 70.0% and 66.7% for the respective treatment groups.

In Study 547 (open label, uncontrolled, non-comparative trial), the clinical success rate in the Clinical PP test of cure population was 85.6% and 76.5% in the ITT population in the Augmentin XR group. The bacteriological success rate in the bacteriological PP test of cure population was 83.0% and 78.1% in the ITT population in the Augmentin XR group.

For PRSP claim, among the 20 patients with CAP due to PRSP (PCN MIC ≥2.0 mcg/ml) who were treated with Augmentin XR, 14 patients were with PCN MIC of 2 and 6 patients with PCN MIC of 4. In the Baceteriological PP, 14/15 (93%) of these isolates were cure (95% CI: 68.1, 99.8) and out of which 10/10 had a penicillin MIC of 2ug/mL (95% CI: 69.2, 99.9) and the remaining 4/5 PRSP isolates had a penicillin MIC of 4ug/mL (95% CI: 28.4, 99.5). In the Bacteriological ITT, 17/20 (85%) of these isolates were cure and out of which 13/14 had a penicillin MIC of 2ug/mL (95% CI: 66.1, 99.8) and the remaining 4/6 PRSP isolates had a penicillin MIC of 4ug/mL(95% CI: 22.2, 95.7). In Table 9, among the patients with Penicillin MIC of 2 ug/ml, 10/16(63%) had Amoxicillin MIC of 2ug/ml and among the patients with Penicillin MIC of 4 ug/ml, only 1/6 (16.6%) had Amoxicillin MIC of 4 ug/ml.

Overall, based on the data, the results have not shown any added benefit of efficacy over Augmentin 875/125mg other than an increased amount of amoxicillin which could have more toxicity issues in the general population. However, based on the data, it can only be concluded that Augmentin XR has some degree of activity in the treatment of CAP caused by penicillin-resistant pneumococcus with PCN MIC of 2ug/ml. There is no adequate/substantial evidence available in support of the efficacy of this drug in the treatment of CAP due to PRSP isolates with PCN MIC≥ 4ug/mL.

It is difficult to make a direct comparison of efficacy of Augmentin XR to other alternate drugs like Levofloxacin for PRSP since it was not used as a comparator in any of these trials. Also, note that the Levofloxacin efficacy does not depend upon the Penicillin MICs.

II. Acute Bacterial Sinusitis (ABS)

In the principal, open label, uncontrolled studies (Study 551 and Study 592), the primary efficacy variable was the per-patient bacteriological response (success/failure) at test of cure in the Bacteriological PP and ITT populations.

The clinical cure rates at the test of cure for both studies in the Clinical PP population were; 92.7% in Study 551 and 94.8% in study 592. The rates in the Clinical ITT population were 87.9% in Study 551 and 88.4% in Study 592.

The bacteriological eradication(cure) rates at test of cure in the Bacteriology PP population were; 93.1% in Study 551 and 96.4% in study 592. The rates in the Bacteriology ITT population were 87.7% in Study 551 and 89.0% in Study 592.

Among the PRSP cases, the bacteriological eradication rates for PRSP (penicillin MIC ≥2ug/mL), there were 36/37 (97.3%) cures in the Bacteriological PP population (95% CI: 85.8, 99.9). Of which, 23/24 (95.8) had a penicillin MIC of 2ug/ml (95% CI: 78.9, 99.9) and 11/11 had a penicillin MIC of 4ug/ml (95% CI: 71.5, 99.9).
In the Bacteriological ITT population, 39/40 (97.5%) were cures (95% CI: 86.8, 99.9). Among the 39 cures, 26/27 (96.3%) had a penicillin MIC of 2ug/ml (95% CI:81.0, 99.9) and 11/11 had a penicillin MIC of 4ug/ml (95% CI: 71.5, 99.9) excluding the two cases with MIC of 8ug/ml and 16 ug/ml.

Excluding the 14 PRSP patients enrolled by Dr. Kim Hendrick, there were 22/23(95.7%) cures in the Bacteriological PP population (95% CI: 78.1, 99.9). Of which 13/14 (92.9) had a penicillin MIC of 2ug/ml (95% CI: 66.1, 99.8) and 7/7 had a penicillin MIC of 4ug/ml (95% CI: 59.0, 99.9 In the Bacteriological ITT population, 25/26 (96.2%) were cures (95% CI: 80.4, 99.9). Among these patients, 16/17 (94.1%) had a penicillin MIC of 2ug/ml (95% CI: 71.3, 99.9) and 7/7 had a penicillin MIC of 4ug/ml (95% CI: 59.0, 99.9).

Among the patients with Penicillin MIC of 2 ug/ml (Table 17), 18/27(66.6%) had Amoxicillin MIC of 2ug/ml and among the patients with Penicillin MIC of 4 ug/ml, only 4/11(36%) had Amoxicillin MIC of 4 ug/ml. The isolates were all obtained from open label studies (study 551 and study 592).

Overall, based on the data provided, it can be concluded that there is better evidence of efficacy (although not substantial due to few isolates presented) in the treatment of ABS as caused by PRSP with penicillin MIC of 2ug/ml.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction

The original submission of GlaxoSmithKline Beecham's New Drug Application for Augmentin XR™ (amoxicillin/clavulanate potassium) Extended Release Tablets (NDA 50-785) was submitted to the Agency on December 20, 2000. As they claim, Augmentin XR (2000/125mg, 16:1 ratio of amoxicillin/clavulanate) was developed specifically for the treatment of Penicillin Resistant Streptococcus Pneumoniae (PRSP) infections involving the respiratory tract. It is a sustained release formulation which is a combination of the semi-synthetic antibiotic, amoxicillin and the beta-lactamase inhibitor clavulanic acid. The sponsor's belief is that by greatly increasing the amoxicillin content of Augmentin, it may be possible to overcome at least some degree of penicillin resistance. In accordance with this concept, Augmentin XR contains a daily dose of 4,000mg of amoxicillin whereas, the already approved Augmentin formulations (4:1 and 7:1 ratios of amoxicillin to clavulanate) contain only 1,500mg and 1,750mg/daily dose of amoxicllin respectively. This NDA was submitted for the indications: Acute Bacterial Sinusitis (ABS), Community-Acquired Pneumonia (CAP) [redacted] due to susceptible strains of common pathogens, including beta-lactamase producing strains of H. influenzae and M. catarrhalis. In the previous submission, the claim for ABS due to PRSP was not considered by the division because of a divisional policy which requires that efficacy for the treatment of PRSP be demonstrated in CAP prior to other respiratory indications. The review was completed and an Action Letter of December 12, 2001 indicated that this product was not approvable.

Based on the meetings and discussions on March 8 and March 21, 2002 which had lead to the resubmission of this package by SmithKline claiming to provide more evidence in support for an approval for CAP and ABS. This was submitted on March 29, 2002.

Augmentin XR is proposed for the treatment of adults with ABS and CAP where the involvement of penicillin-resistant *Streptococcus pneumoniae* (PRSP) as well as beta-lactamase producing bacteria is known or suspected.

The sponsor submitted Integrated Summary of Efficacy (ISE) of the clinical program that supports the efficacy of Augmentin XR as an antibacterial agent for use in the respiratory tract infections of CAP and ABS. However, the focus of this review will be mainly on the efficacy of patients with CAP and ABS due to PRSP.

2.2 Overview of the Clinical Program and Studies Reviewed

Community-acquired Pneumonia (CAP)

Principal Controlled Studies in CAP

BRL-025000/546 A randomized, double-blind, double-dummy, multicenter parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days versus oral Augmentin 875/125mg twice daily for 7 days in the treatment of bacterial CAP in adults. (Results of this study were reported in full to NDA 50-785, as submitted on December 20, 2000.)

BRL-025000/556 A randomized, double-blind, double-dummy, multicenter, parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days versus oral Augmentin 1000/125mg three times daily for 10 days in the treatment of bacterial CAP in adults. (Results of this study were reported in full to NDA 50-785, as submitted on December 20, 2000.)

BRL-025000/557 A randomized, double-blind, double-dummy, multicentre, parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily versus oral Augmentin 875/125mg three times daily for 7 or 10 days for the treatment of bacterial CAP in adults.

Principal Uncontrolled Study in CAP- 2nd Interim Report

BRL-025000/547 An open, non-comparative, multicenter study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days for the treatment of bacterial CAP in adults. (Results of the first interim analysis [Clinical cut-off: June19 2000] of this study were reported in full to NDA 50-785, as submitted on December 20, 2000.)

On February 23, 2001, the Division requested a re-analysis of efficacy results reported in NDA 50-785 excluding the patients enrolled by three investigators, Drs. C. Andrew DeAbate, C. P. Mathew and Dr. William N. Sokol. The investigator Dr. William N. Sokol obtained samples for bacteriologic assessment via sinus endoscopy rather than maxillary sinus puncture.

Acute Bacterial Sinusitis (ABS).

Principal Controlled Study in ABS

BRL-025000/550 A randomized, double-blind, double-dummy, multicenter parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days versus oral levofloxacin 500mg once daily for 10 days in the treatment

of ABS in adults. (Results of this study were reported in full to NDA 50-785, as submitted on December 20, 2000.)

Statistical Reviewer's Comment:

In Study 550, specimen collection was done by sinus endoscopy or rhinoscopy and was only conducted at selected study centers. Specimens obtained by antral puncture is the preferred method for accurate microbial diagnosis in sinusitis and the microbiology data from study 550 was not included in this review.

Principal Uncontrolled Studies in ABS

BRL-025000/551 An open, non-comparative, multicenter study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days for the treatment of ABS in adults. (Results of this study were reported in full to NDA 50-785, as submitted on December 20, 2000.)

BRL-025000/592 An open, non-comparative, multicenter study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days for the treatment of ABS in adults.

Statistical Reviewer's Comment:

For ABS, additional analyses were performed after excluding the patients enrolled by Dr. Kim Hendrick in addition to the other excluded investigators (Drs. C. Andrew DeAbate, C. P. Mathew and Dr. William N. Sokol). There were 14 patients with PRSP enrolled by Dr. Kim Hendrick from sites 223 and 021. There were 11 patients from site 223 and 3 patients from site 021.

2.3 Statistical Evaluation of Evidence on Efficacy

2.3.1 Community Acquired Pneumonia (CAP)

Study Design and Methodology

There were three Principal controlled studies (studies 546, 556 and 557) and one uncontrolled study 547 submitted for CAP indication. The three principal controlled CAP studies (Studies 546, 556 and 557) were randomized, multicenter, double-blind, double-dummy, parallel group studies designed to evaluate the clinical and bacteriological efficacy and safety of Augmentin XR in comparison with Augmentin regimens used in clinical practice.

In Study 546, a 7 day course of Augmentin XR was compared with amoxicillin/ clavulanate 875/125mg (7:1) bid for 7 days, which is the conventional Augmentin

formulation currently used in the US for the treatment of CAP. In study 557, Augmentin XR was compared with Augmentin 875/125mg (7:1) tid, which is the approved Augmentin dosage regimen for CAP in Spain and Italy. The treatment duration was routinely to be for 7 days, but this could be extended to 10 days if the patient had a severe infection, or for other reasons, based on the judgement of the investigator at the on-therapy visit.

In Study 556, Augmentin XR was compared with Augmentin 1000/125mg (8:1) tid, which is the approved Augmentin dosage regimen for CAP in France, one of the principal countries involved in the study. In Study 556, a 10 day regimen of Augmentin 1000/125mg tid was compared with a 10 day regimen of Augmentin XR and this regimen is not approved in the US.

Male and female patients (aged ≥16 years in Study 546 and aged ≥18 years in Studies 556 and 557) with a clinical and radiological diagnosis of CAP, were recruited into the controlled CAP studies. The principal entry criteria are summarized as follows:

- a chest radiograph within the 48 hour period prior to randomization showing the presence of new or progressive infiltrate(s) or consolidation consistent with pneumonia,

- a fever (as defined for each study) or history of fever for the current CAP infection,

- at least one (Studies 546 and 557) or two (Study 556) of the following additional signs or symptoms of CAP: - new or increased cough - purulent sputum or a change in sputum characteristics - auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation - dyspnea or tachypnea (Study 546).

Efficacy Variables

The primary efficacy variable in the three principal controlled CAP studies was the clinical response (success or failure) at test of cure.

For patients who were clinical successes at end of therapy, clinical response at test of cure was determined based on the changes in signs and symptoms of CAP from the screening assessment, leading first to the assignment of a clinical outcome by the investigator i.e., clinical success, clinical recurrence or unable to determine.

The sponsor defined "clinical failure" of patients with community acquired pneumonia in such a way as to distinguish between those patients with true failure and those who only had symptomatic sequelae of community acquired pneumonia. The sponsor's definitions of "Success" and "Failure" are included below.

- Clinical Success: Sufficient resolution of the signs and symptoms of CAP for patients who were clinical successes at the end of therapy visit such that no additional antibacterial therapy was indicated for CAP.

- Clinical Failure: Reappearance or deterioration of the signs and symptoms of CAP for patients who were clinical successes at the end of therapy visit such that additional antibacterial therapy was indicated for CAP.

- Unable to Determine: An assessment of clinical outcome could not be made, eg: the patient was lost to follow-up or did not consent to clinical examination.

The medical officer accepts the sponsor's definition of clinical success and failure as valid. Among the twenty patients of PRSP, except for two patients, the TOC visits ranged from 17 to 28 days after the End of Therapy. There were two patients (547.110.18283 and 547.437.18569) who were considered ITT failures who did not have a TOC visit.

In Studies 546, 556 and 557, patients were randomized on a 1:1 basis to receive treatment with either Augmentin XR or a comparator Augmentin regimen. In Study 546, a total of 516 patients were randomized to study treatment (Augmentin XR: 255 patients, Augmentin 875/125mg bid: 261 patients). There were 514 patients in the ITT population of this study since two patients in the Augmentin 875/125mg bid group withdrew prior to receiving any study medication (one patient withdrew consent, and one patient was withdrawn due to an adverse experience). In Study 556, a total of 347 patients were randomized to study treatment (Augmentin XR: 169 patients, Augmentin 1000/125mg: 178 patients). There were 344 patients in the ITT population since three patients in the Augmentin 1000/125mg group were withdrawn prior to receiving study medication (for positive *Legionella* urine antigen, pulmonary abscess and protocol deviation). In Study 557, 320 patients were randomized to study treatment (Augmentin XR: 158 patients, Augmentin 875/125mg tid: 162 patients). According to the sponsor, there were 319 patients in the ITT population of this study since one patient in the Augmentin 875/125mg tid group withdrew consent before receiving any study medication.

A similar number of patients withdrew from Studies 546, 556 and 557; 59 patients (11.5%) withdrew from Study 546 (Augmentin XR: 28/255, 11.0%, Augmentin 875/125mg bid: 31/259, 12.0%), 51 patients (14.8%) withdrew from Study 556 (Augmentin XR: 28/169, 16.6%, Augmentin 1000/125mg: 23/175, 13.1%) and 50 patients (15.7%) withdrew from Study 557 (Augmentin XR: 22/158, 13.9%, Augmentin 875/125mg tid: 28/161, 17.4%).

Statistical Reviewer's Comments

In comparative trials, testing the equivalence of treatment differences with respect to the efficacy variables were assessed based on a two-tailed 95% confidence interval of the difference in clinical and microbiological cure rates. The primary efficacy analysis would be evaluated using a non-inferiority margin (delta) of 10%. The robustness of the primary efficacy analysis will be assessed using the Clinically/Microbiologically Evaluables (CE) and the ITT and/or the MITT populations.

2.3.1.1 Demographics and Baseline Characteristics

Table 1: Demographic Characteristics: CAP Principal Controlled Studies 546, 556 and 557 (Clinical ITT Test of Cure Population)

Demographic Characteristics	Study 546		Study 556		Study 557	
	Augmentin XR 2000/125mg bid	Augmentin 875/125mg bid	Augmentin XR 2000/125mg bid	Augmentin 1000/125mg bid	Augmentin XR 2000/125mg bid	Augmentin 875/125mg bid
	N=255	N=259	N=169	N=175	N=158	N=161
Gender, n (%)						
Male	130 (51.0)	127 (49.0)	93 (55.0)	103 (58.9)	109 (69.0)	110 (68.3)
Female	125 (49.0)	132 (51.0)	76 (45.0)	72 (41.1)	49 (31.0)	51 (31.7)
Race, n (%)						
White	211 (82.7)	223 (86.1)	156 (92.3)	165 (94.3)	154 (97.5)	159 (98.8)
Black	20 (7.8)	14 (5.4)	5 (3.0)	4 (2.3)	1 (0.6)	1 (0.6)
Oriental	3 (1.2)	1 (0.4)	1 (0.6)	1 (0.6)	0	0
Other	21 (8.2)	21 (8.1)	7 (4.1)	5 (2.9)	3 (1.9)	1 (0.6)
Age (yrs)						
Mean (SD)	52.0 (17.8)	52.5 (17.6)	57.3 (18.6)	56.9 (19.1)	56.6 (20.1)	53.5 (19.5)
Range	17-90	16-91	19-92	18-89	19-92	18-94

Statistical Reviewers Comments:

In the ITT population above, the majority of patients were white in all three studies but the proportion was less overall in Study 546 (84.4%, 434/514) compared with Study 556 (93.3%, 321/344) and Study 557 (98.1%, 313/319). In Study 546 approximately half of the patients were male (Augmentin XR: 51.0%; Augmentin 875/125mg: 49.0%), while in Study 556 there was a slightly higher proportion of males (Augmentin XR: 55.0%; Augmentin 1000/125mg: 58.9%) and an even higher proportion of males in Study 557 (Augmentin XR: 69.0%; Augmentin 875/125mg: 68.3%). In Study 546, the mean age of patients was 52.0 years in the Augmentin XR group and 52.5 years in the Augmentin 875/125mg group. The mean age in Studies 556 and 557 was slightly higher; Study 556: 57.3 years in the Augmentin XR group and 56.9 years in the Augmentin 1000/125mg group; Study 557, 56.6 years and 53.5 years, respectively.

Table 2: Demographic Characteristics: CAP Uncontrolled Study 547 (ITT and Bacteriology ITT Populations)

Demographic Characteristic	**Augmentin XR 2000/125mg bid 7 days ITT N=1122**		**Bacteriology ITT N=342**	
Gender, n (%)				
Male	649	(57.8)	226	(66.1)
Female	473	(42.2)	116	(33.9)
Race, n (%)				
White	610	(54.4)	218	(63.7)

Black	139	(12.4)	45	(13.2)
Oriental	207	(18.4)	45	(13.2)
Other*	166	(14.8)	34	(9.9)
Age (yrs)				
Mean (SD)		47.4 (18.8)		47.1 (19.4)
Range		16.0-98.0		16.0-98.0

Statistical Reviewers Comments:

In both the Bacteriology ITT and ITT populations, there was a higher proportion (66.1% and 57.8%) of males than female. The mean age of patients in the Bacteriology ITT population and in the ITT population was approximately 47 years. The proportions of white compared to other ethnic groups in both populations were higher. The proportion of patients in the Bacteriology ITT population hospitalized for treatment was 40.5% (454/1122) and 45.9% (157/342) in the ITT population.

2.3.1.2 Patient Disposition

Table 3: Patient Disposition: CAP Principal Controlled Studies 546, 556 and 557

	Study 546				Study 556				Study 557			
	Augmentin XR 2000/125mg bid (7 days)		Augmentin 875/125mg bid (7 days)		Augmentin XR 2000/125mg bid (10 days)		Augmentin 1000/125mg tid (10 days)		Augmentin XR 2000/125mg bid (7 or 10 days)		Augmentin 875/125mg tid (7 or 10 days)	
	n		n		n		n		n		n	
Randomized	255		261		169		178		158		162	
Received Study Medication (ITT)	255		259		169		175		158		161	
Completed Study	227		228		141		152		136		133	
Reason for Withdrawal (ITT), n (%):												
Adverse Experience	10	(3.9)	19	(7.3)	9	(5.3)	7	(4.0)	11	(7.0)	9	(5.6)
Insufficient Therapeutic Effect	2	(0.8)	1	(0.4)	5	(3.0)	5	(2.9)	5	(3.2)	8	(5.0)
Protocol Deviation	2	(0.8)	1	(0.4)	6	(3.6)	5	(2.9)	2	(1.3)	5	(3.1)
Lost to Follow-Up	11	(4.3)	10	(3.9)	6	(3.6)	4	(2.3)	3	(1.9)	4	(2.5)
Other Reason	3	(1.2)	0	-	2	(1.2)	2	(1.1)	1	(0.6)	2	(1.2)
Total Withdrawn, n (%)	28	(11.0)	31	(12.0)	28	(16.6)	23	(13.1)	22	(13.9)	28	(17.4)
Populations for Analysis												
Clinical PP at End of Therapy	221		219		129		119		126		128	
Clinical PP at Test of Cure	204		204		118		114		114		116	
Bacteriology ITT	39		30		44		47		30		30	
Bacteriology PP at End of Therapy	33		26		33		34		23		26	
Bacteriology PP at Test of Cure	32		26		32		32		20		22	

Sponsor's Table

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Table 4: Patient Disposition: CAP Uncontrolled Study 547 (All Enrolled Patients)

	Augmentin XR 2000/125mg bid 7 days			
	All Patients	Pre-Amendment Subgroup	Post-Amendment Subgroup*	*S. pneumoniae* Population
Population	**n**	**n**	**n**	**n**
Enrolled	1125	917	208	163
Received Study Medication (ITT)	1122	914	208	163
Completed Study	924	764	160	143
Clinical PP End of Therapy	929	760	169	140
Clinical PP Test of Cure	842	691	151	131
Bacteriology ITT	342	265	77	163
Bacteriology PP End of Therapy	293	229	64	140
Bacteriology PP Test of Cure	271	216	55	131

Sponsor's Table

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ON ORIGINAL

According to the sponsor, in Studies 546, 556 and 557, patients were randomized on a 1:1 basis to receive treatment with either Augmentin XR or a comparator Augmentin regimen. In Study 546, a total of 516 patients were randomized to study treatment (Augmentin XR: 255 patients, Augmentin 875/125mg bid: 261 patients). There were 514 patients in the ITT population of this study since two patients in the Augmentin 875/125mg bid group withdrew prior to receiving any study medication (one patient withdrew consent, and one patient was withdrawn due to an adverse experience). In Study 556, a total of 347 patients were randomized to study treatment (Augmentin XR: 169 patients, Augmentin 1000/125mg: 178 patients). There were 344 patients in the ITT population since three patients in the Augmentin 1000/125mg group were withdrawn prior to receiving study medication (for positive *Legionella* urine antigen, pulmonary abscess and protocol deviation). In Study 557, 320 patients were randomized to study treatment (Augmentin XR: 158 patients, Augmentin 875/125mg tid: 162 patients). There were 319 patients in the ITT population of this study since one patient in the Augmentin 875/125mg tid group withdrew consent before receiving any study medication.

In study 547, a total of 1125 patients were included in the second interim analysis which was comprised of patients who had completed all study visits on or before July 5, 2001, and whose data had been received by GSK. Of these 1125 patients, 1122 patients received study medication and were included in the ITT population. Two patients were enrolled into the study but did not receive study medication and were therefore not included in the ITT population. An additional patient was lost to follow-up after the screening visit; as no information was recorded in the CRF for this patient after the screening visit, this patient was excluded from the ITT population. In the ITT population, 924/1122 patients (82.4%) completed the study. One hundred and ninety-eight patients (17.6%) withdrew from the study. According to the sponsor, the most frequently reported reason for withdrawal was adverse experiences (63 patients, 5.6%).

In these studies, patients were included in the Bacteriology ITT population provided that they had at least one typical pre-therapy pathogenic organism obtained from culture of sputum, other respiratory sample or blood. An organism isolated from a sputum sample was only to be treated as a pathogen if >25 WBCs and <10 epithelial cells per field at 100x magnification were observed on Gram stain. This criterion did not apply to respiratory samples obtained by invasive procedures or to *Legionella* cultures. According to the sponsor's submission, in Study 546, 69 patients (13.4%) were included in the Bacteriology ITT population (39 patients in the Augmentin XR group and 30 patients in the Augmentin 875/125mg bid group), in Study 556, 91 patients (26.5%) comprised the Bacteriology ITT population (44 patients in the Augmentin XR group and 47 patients in the Augmentin 1000/125mg group) and in Study 557, 60 patients (18.8%) comprised the Bacteriology ITT population (30 patients in the Augmentin XR group and 30 patients in the Augmentin 875/125mg tid group).

This review would be based on M.O's re-defined clincial and microbiological population for PRSP cases.

2.3.1.3 Efficacy Results

Table 5: Summary of Clinical and Bacteriological Response at Test of Cure: Principal CAP Studies 546, 547, 556 and 557 (All Populations)

	Success Rate		
	Augmentin XR	Augmentin*	Treatment Difference
	% (n/N)	% (n/N)	% (95% CI)
CLINICAL RESPONSE (PRIMARY PARAMETER)			
Clinical PP Population			
Study 546	86.3% (176/204)	91.2% (186/204)	-4.9 (-11.0, 1.2)
Study 556	91.5% (108/118)	93.0% (106/114)	-1.5 (-8.3, 5.4)
Study 557	94.7% (108/114)	88.8% (103/116)	5.9 (-1.1, 13.0)
Study 547	85.6% (721/842)	-	(83.0, 87.9)
ITT Population			
Study 546	78.0% (199/255)	82.6% (214/259)	-4.6 (-11.4, 2.3)
Study 556	81.1% (137/169)	85.7% (150/175)	-4.6 (-12.5, 3.2)
Study 557	84.8% (134/158)	77.0% (124/161)	7.8 (-0.8, 16.4)
Study 547	76.5% (858/1122)	-	(73.9, 78.9)
BACTERIOLOGICAL RESPONSE			
Bacteriology PP Population			
Study 546	78.1% (25/32)	84.6% (22/26)	-6.5 (-26.4, 13.4)
Study 556	90.6% (29/32)	84.4% (27/32)	6.3 (-9.9, 22.4)
Study 557	85.0% (17/20)	77.3% (17/22)	7.7 (-15.8, 31.2)
Study 547	83.0% (225/271)	-	(77.9, 87.2)
Bacteriology ITT Population			
Study 546	69.2% (27/39)	83.3% (25/30)	-14.1 (-33.8, 5.6)
Study 556	84.1% (37/44)	76.6% (36/47)	7.5 (-8.7, 23.7)
Study 557	70.0% (21/30)	66.7% (20/30)	3.3 (-20.2, 26.9)
Study 547	78.1% (267/342)	-	(73.2, 82.3)

* Comparators were Augmentin 875/125mg bid for 7 days (Study 546), Augmentin 1000/125mg tid for 10 days (Study 556) and Augmentin 875/125mg tid for 7 or 10 days (Study 557).

In study 546, in the Clinical PP population at test of cure visit, the clinical success rates were; (86.3% in the Augmentin XR group and 91.2% in the Augmentin 875/125mg group). In the ITT population, the clinical success rate at test of cure was 78.0% for Augmentin XR and 82.6% for Augmentin 875/125mg. In both populations, the lower limit of the 95% CI (-11.0, 1.2 for the Clinical PP analysis and -11.4, 2.3 for the ITT analysis) fell outside the non-inferiority limit of -10% and failed to demonstrate non-inferiority (Table 5).

In Study 556, the clinical success rate at test of cure for the Clinical PP population was 91.5% for Augmentin XR and 93.0% for Augmentin 1000/125mg. Results in the ITT population were 81.1% and 85.7% in the respective treatment groups. The clinical response in the PP population for Augmentin XR 2000/125mg bid was concluded to be as good as Augmentin 1000/125mg tid (95% CI: -8.3, 5.4) using a non-inferiority margin of 10% but failed to demonstrate non-inferiority in the ITT population (95% CI: -12.5, 3.2).

In Study 557, the clinical success rate in the Clinical PP test of cure population was 94.7% in the Augmentin XR group and 88.8% in the Augmentin 875/125mg group. Results in the ITT population were 84.8% and 77.0% in the respective treatment groups. In each population, the clinical efficacy of Augmentin XR was concluded to be at least as good as that of Augmentin 875/125mg, based on using a non-inferiority margin of 10% (95% CI: -1.1, 13.0 for Clinical PP and –0.8, 16.4 for the ITT analyses).

In Study 547 (open label, uncontrolled, non-comparative trial), the clinical success rate in the Clinical PP test of cure population was 85.6% and 76.5% in the ITT population in the Augmentin XR group.

The bacteriological success rates in study 546 for the Bacteriology PP population were 78.1% in the Augmentin XR group and 84.6% in the Augmentin 875/125mg group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 69.2% in the Augmentin XR group and 83.3% in the Augmentin 875/125mg group. The 95% confidence limits for all the studies are given in Table 5 for reference.

In Study 556, the bacteriological success rates at test of cure for the Bacteriology PP population were 90.6% in the Augmentin XR group and 84.4% in the Augmentin 1000/125mg group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 84.1% in the Augmentin XR group and 76.6% in the Augmentin 1000/125mg group.

The bacteriological success rates at test of cure for the Bacteriology PP population in Study 557 were 85.0% in the Augmentin XR group and 77.3% in the Augmentin 875/125mg group. In the Bacteriology ITT population the bacteriological success rates were 70.0% and 66.7% for the respective treatment groups.

In Study 547 (open label, uncontrolled, non-comparative trial), the bacteriological success rate in the bacteriological PP test of cure population was 83.0% and 78.1% in the ITT population in the Augmentin XR group.

Patients with CAP due to PRSP

The bacteriological outcome for PRSP(penicillin MIC ≥2ug/mL), for the pooled Augmentin XR group from Studies 546, 547, 556 and 557, and the pooled comparator Augmentin group from Studies 546, 556 and 557 (i.e. Augmentin 875/125mg bid, Augmentin 1000/125 mg tid and Augmentin 875/125mg tid) are provided below based on sponsor's submission. Five of these patients were from the original NDA and the remaining 15 patients were accrued through the ongoing open label, non-comparative Augmentin XR study (Study 547) and from one completed active comparator controlled study (Study 557).

Table 6: Number (%) of Key Pathogens with Bacteriological Outcome of Eradicated or Presumed Eradicated by Selected Resistant Pathogen and Beta-Lactamase Production at Test of Cure: Combined CAP Studies 546, 547, 556 and 557 (Bacteriology PP and Bacteriology ITT Populations)

	Combined CAP 7 and 10 Day Studies 546, 547, 556 and 557			
	Augmentin XR		**Augmentin Comparators**	
	N=355		**N=80**	
	n/N*	**%**	***n/N****	**%**
Bacteriology PP				
Penicillin-resistant *S. pneumoniae* (MIC ≥2ug/mL)	14/15	(93.3)	3/4	(75.0)
Bacteriology ITT	**N=455**		**N=107**	
Penicillin-resistant *S. pneumoniae* (MIC ≥2ug/mL)	17/22	(77.3)	3/6	(50.0)

Sponsor's Table (only Penicillin-resistant *S. pneumoniae* (MIC ≥2ug/mL included in this review)
* *n/N* = number of isolates which were eradicated or presumed eradicated / number of isolates with MIC or beta-lactamase data for the pathogen.
Augmentin Comparators=Augmentin 875/125 mg bid (Study 546) Augmentin 1000/125 mg tid (Study 556) and Augmentin 875/125mg tid (Study 557)

Among the 20 patients with CAP due to PRSP (PCN MIC ≥2.0 mcg/ml) who were treated with Augmentin XR, 14 patients were with PCN MIC of 2 and 6 patients with PCN MIC of 4.

According to the sponsor's Table 7, four patients presented with PRSP bacteremic pneumonia. In the PP analysis, 2/2 (100%) patients with bacteremia caused by penicillin-

resistant *S. pneumoniae* were evaluated as clinical successes. In the ITT analysis, of 4 patients with penicillin-resistant *Streptococcus pneumoniae*, 2 were clinical successes at TOC. Of the remaining two patients, one HIV positive patient was an End of Therapy success, but subsequently was lost to follow-up prior to the TOC visit (designated outcome was unable to determine, response of failure). The other patient was non-compliant with the first 72 hours of treatment and was an EOT failure. Notably, all four patients had negative on-therapy blood cultures.

Table 7: Clinical Success Rate at Test of Cure in All Bacteremic Patients: Combined CAP Studies 546, 547, 556 and 557 (Bacteriology PP and ITT Populations)

	Bacteriology PP		**Bacteriology ITT**	
	n/N	(%)	n/N	(%)
Bacteremia Overall	31/37	(83.8)	37/52	(71.2)
S. pneumoniae Bacteremia	24/28	(85.7)	28/38	(73.7)
PRSP Bacteremia	2/2	(100)	2/4	(50.0)

Sponsor's Table

Statistical Reviewer's Comments

According to the sponsor's results, 31/37 (83.8%) bacteremic pneumonia patients among the Bacteriology PP population and 37/52 (71.2%) among the Bacteriological ITT population were clinical successes. There were 24/28 (85.7%) among the Bacteriology PP patients and 28/38 (73.7%) among the Bacteriology ITT patients with S. pneumoniae Bacteremia who were clinical successes. Four patients presented with PRSP bacteremic pneumonia. In the PP analysis, 2 patients with bacteremia caused by penicillin-resistant S. pneumoniae were evaluated as clinical successes. In the ITT analysis, of 4 patients with penicillin-resistant Streptococcus pneumoniae, 2 were clinical successes at TOC. Please note that it is a small number to make any strong and meaningful conclusion.

Table 8: Bacteriological Responses of Augmentin XR for CAP (studies 546, 547, 556 and 557 combined) due to PRSP- M.O. Reclassification

	n/M	(%)	95% CI[a]
Bacteriological PP	14/15	(93)	(68.1, 99.8)
MIC=2	10/10	(100)	(69.2, 99.9)
MIC=4	4/5	(80)	(28.4, 99.5)
Bacteriological ITT	17/20	(85)	(62.1, 96.8)
MIC=2	13/14	(92.9)	(66.1, 99.8)
MIC=4	4/6	(66.7)	(22.2, 95.7)

[a] 95% CIs are calculated using exact probabilities

Statistical Reviewer's Comments:

Among the 20 isolates of S. pneumoniae were resistant to penicillin (penicillin MIC ≥2ug/mL). In the Baceteriological PP, 14/15 (93%) of these isolates were cure and out of which 10/10 had a penicillin MIC of 2ug/mL (95% CI: 69.2, 99.9) and the remaining 4/5 PRSP isolates had a penicillin MIC of 4ug/mL(95% CI: 28.4, 99.5) In the Bacteriological ITT, 17/20 (85%) of these isolates were cure and out of which 13/14 had a penicillin MIC of 2ug/mL (95% CI: 66.1, 99.8) and the remaining 4/6 PRSP isolates had a penicillin MIC of 4ug/mL(95% CI: 22.2, 95.7). Although the fewer number of isolates do not provide any strong statistical evidence to the reviewer, it can be concluded that the efficacy is better for penicillin MIC of 2ug/mL than penicillin MIC of 4ug/mL.

Table 9: Relationship Between Penicillin MIC and Amoxicillin MIC for PRSP Isolates of CAP Patients

		Penicillin MIC of PRSP Isolate	
		2.0 ug/ml	4.0 ug/ml
Amox MIC	1.0 ug/ml	4	0
	2.0 ug/ml	10	2
	4.0 ug/ml	1	1
	8.0 ug/ml	1	3
	Total	**16**	**6**

M.O.'s Table

Statistical Reviewer's Comments:

Among MIC≤4, 11/22 (50%) of isolates had MIC's for penicillin which matched those for amoxicillin. Among the patients with Penicillin MIC of 2 ug/ml, 10/16(63%) had Amoxicillin MIC of 2ug/ml and among the patients with Penicillin MIC of 4 ug/ml, only 1/6 (16.6%) had Amoxicillin MIC of 4 ug/ml.

2.3.1.4 Conclusions and Recommendations

There were three Principal controlled studies (studies 546, 556 and 557) and one uncontrolled study 547 submitted for CAP indication.

In Study 546, a 7 day course of Augmentin XR was compared with amoxicillin/ clavulanate 875/125mg (7:1) bid for 7 days, which is the conventional Augmentin formulation currently used in the US for the treatment of CAP. In study 557, Augmentin

XR was compared with Augmentin 875/125mg (7:1) tid, which is the approved Augmentin dosage regimen for CAP in Spain and Italy but not in US. In Study 556, Augmentin XR was compared with Augmentin 1000/125mg (8:1) tid, which is the approved Augmentin dosage regimen for CAP in France.

The principal conclusions of the overall efficacy assessment of Augmentin XR in CAP were based on the clinical and microbiological cure rates at the Test of Cure Visit.

In study 546, in the Clinical PP population at test of cure visit, the clinical success rates were; (86.3% in the Augmentin XR group and 91.2% in the Augmentin 875/125mg group). In the ITT population, the clinical success rate at test of cure was 78.0% for Augmentin XR and 82.6% for Augmentin 875/125mg. In both populations(95% CIs: -11.0, 1.2 for the Clinical PP analysis and -11.4, 2.3 for the ITT analysis) Augmentin XR failed to demonstrate non-inferiority to Augmentin 875/125 (Table 5), using a non-inferiority margin of 10%.

The bacteriological success rates in study 546 for the Bacteriology PP population were 78.1% in the Augmentin XR group and 84.6% in the Augmentin 875/125mg group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 69.2% in the Augmentin XR group and 83.3% in the Augmentin 875/125mg group. The 95% confidence limits for all the studies are given in Table 5 for reference.

In Study 556, the clinical success rate at test of cure for the Clinical PP population was 91.5% for Augmentin XR and 93.0% for Augmentin 1000/125mg. Results in the ITT population were 81.1% and 85.7% in the respective treatment groups. The clinical response in the PP population for Augmentin XR 2000/125mg bid was concluded to be as good as Augmentin 1000/125mg tid (95% CI: -8.3, 5.4). In the ITT population, Augmentin XR 2000/125mg failed to demonstrate non-inferiority (95% CI: -12.5, 3.2), using a non-inferiority margin of 10%.

In Study 556, the bacteriological success rates at test of cure for the Bacteriology PP population were 90.6% in the Augmentin XR group and 84.4% in the Augmentin 1000/125mg group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 84.1% in the Augmentin XR group and 76.6% in the Augmentin 1000/125mg group.

In Study 557, the clinical success rate in the Clinical PP test of cure population was 94.7% in the Augmentin XR group and 88.8% in the Augmentin 875/125mg group. Results in the ITT population were 84.8% and 77.0% in the respective treatment groups. In each population, the clinical efficacy of Augmentin XR was concluded to be at least as good as that of Augmentin 875/125mg, based on using a non-inferiority margin of 10% (95% CI: -1.1, 13.0 for Clinical PP and -0.8, 16.4 for the ITT analyses).

The bacteriological success rates at test of cure for the Bacteriology PP population in Study 557 were 85.0% in the Augmentin XR group and 77.3% in the Augmentin

875/125mg group. In the Bacteriology ITT population the bacteriological success rates were 70.0% and 66.7% for the respective treatment groups.

In Study 547 (open label, uncontrolled, non-comparative trial), the clinical success rate in the Clinical PP test of cure population was 85.6% and 76.5% in the ITT population in the Augmentin XR group. The bacteriological success rate in the bacteriological PP test of cure population was 83.0% and 78.1% in the ITT population in the Augmentin XR group.

For PRSP claim, among the 20 patients with CAP due to PRSP (PCN MIC ≥2.0 mcg/ml) who were treated with Augmentin XR, 14 patients were with PCN MIC of 2 and 6 patients with PCN MIC of 4. In the Baceteriological PP, 14/15 (93%) of these isolates were cure (95% CI: 68.1, 99.8) and out of which 10/10 had a penicillin MIC of 2ug/mL (95% CI: 69.2, 99.9) and the remaining 4/5 PRSP isolates had a penicillin MIC of 4ug/mL (95% CI: 28.4, 99.5). In the Bacteriological ITT, 17/20 (85%) of these isolates were cure and out of which 13/14 had a penicillin MIC of 2ug/mL (95% CI: 66.1, 99.8) and the remaining 4/6 PRSP isolates had a penicillin MIC of 4ug/mL(95% CI: 22.2, 95.7). In Table 9, among the patients with Penicillin MIC of 2 ug/ml, 10/16(63%) had Amoxicillin MIC of 2ug/ml and among the patients with Penicillin MIC of 4 ug/ml, only 1/6 (16.6%) had Amoxicillin MIC of 4 ug/ml.

Overall, based on the data, the results have not shown any added benefit of efficacy over Augmentin 875/125mg other than an increased amount of amoxicillin which could have more toxicity issues in the general population. However, based on the data, it can only be concluded that Augmentin XR has some degree of activity in the treatment of CAP caused by penicillin-resistant pneumococcus with PCN MIC of 2ug/ml. There is no adequate/substantial evidence available in support of the efficacy of this drug in the treatment of CAP due to PRSP isolates with PCN MIC≥ 4ug/mL.

It is difficult to make a direct comparison of efficacy of Augmentin XR to other alternate drugs like Levofloxacin for PRSP since it was not used as a comparator in any of these trials. Also, note that the Levofloxacin efficacy does not depend upon the Penicillin MICs.

2.3.2 Acute Bacterial Sinusitis (ABS)

For this resubmission, the reviewer's main focus would be on the issue of efficacy of Augmentin XR for the treatment of ABS due to PRSP based on the data submitted from two open label studies 551 and 592.

Study 551 was a non-comparative trial designed to assess the bacteriological and clinical efficacy and safety of oral Augmentin XR for 10 days in the treatment of patients with ABS, particularly those with penicillin-resistant *S. pneumoniae* (PRSP) with amoxicillin/clavulanic acid MICs of at least 4ug/ml.

Study 592 was an open label, non-comparative trial also designed to assess the bacteriological and clinical efficacy and safety of oral Augmentin XR for 10 days in the treatment of patients with ABS, particularly those with PRSP. Although this principal study was still ongoing at the time of the clinical cut off for this submission, data from a prospectively defined interim analysis (based on August 2, 2001, cut off for completion of study visits) are included in this summary.

The primary efficacy variable in these principal uncontrolled studies would be the per-patient bacteriological response (success or failure) at test of cure for the Bacteriology PP and ITT populations. The bacteriological evaluation was based on the assessment of pathogens isolated from sinus puncture samples collected from all patients at screening and at the time of any clinical failure.

The study visits were the same for both studies i.e., after screening (Day 0), patients were expected to attend clinic on-therapy (Day 3-5), at end of therapy (Day 12-14), and at test of cure (Day 17-24).

The primary efficacy variable was the per-patient bacteriological response (success or failure) at test of cure (Visit 4), determined from the per pathogen bacteriolgical outcome information on initial and new pathogens. The per patient bacteriological response (success or failure) at test of cure combined information on initial and new pathogens as follows:

- *Success*: All initial pathogens were eradicated or presumed eradicated at test of cure, without any new infection, with or without colonization.

- *Failure*: Failure or presumed failure of one or more of the initial pathogens at test of cure, a new infection or an assessment of unable to determine for one or more initial pathogens.

Clinical response (success or failure) to study medication at test of cure (Visit 4) was a secondary efficacy variable. The investigator evaluated each patient's clinical outcome by comparing the signs and symptoms at the end of therapy visit with those observed at

the test of cure visit. Patients whose clinical outcome was 'unable to determine' were excluded from the Clinical PP population.

2.3.2.1 Demographic and Baseline Characteristics

Table 10: Demographic Characteristics: ABS Principal Uncontrolled Studies 551 and 592 (ITT and Bacteriology ITT Populations)

	Augmentin XR 2000/125mg bid			
	Study 551		Study 592	
Demographic Characteristics	**ITT N=804**	**Bacteriology ITT N=359**	**ITT N=861**	**Bacteriology ITT N=465**
Gender, n (%)				
Male	347 (43.2)	159 (44.3)	329 (38.2)	171 (36.8)
Female	457 (56.8)	200 (55.7)	532 (61.8)	294 (63.2)
Race, n (%)				
White	720 (89.6)	327 (91.1)	775 (90.0)	442 (95.1)
Black	41 (5.1)	15 (4.2)	25 (2.9)	10 (2.2)
Oriental	3 (0.4)	1 (0.3)	6 (0.7)	1 (0.2)
Other*	40 (5.0)	16 (4.5)	55 (6.4)	12 (2.6)
Age, (yrs)				
Mean (SD)	40.8 (13.7)	40.7 (14)	40.4 (14.4)	40.8 (14.2)
Range	16-83	16-83	16-87	16-83

Sponsor's Table

Statistical Reviewer's Comments:

Comparing both studies for differences in demographic characteristics between the ITT and the Bacteriology ITT populations, there was a slightly higher proportion of females than males and more than 89% of patients in both populations were white. The mean age of patients in both studies was approximately 40 years.

2.3.2.2 Patient Disposition

Table 11: Patient Disposition: ABS Principal Uncontrolled Studies 551 and 592

(All Enrolled Patients)

Population	**Study 551 Augmentin XR 2000/125mg**	**Study 592 Augmentin XR 2000/125mg**
Enrolled	806	861
Received Study Medication (ITT)	804	861
Completed Study	754	804
Bacteriology ITT	359	465
Bacteriology PP at End of Therapy	327	406
Bacteriology PP at Test of Cure	321	387
Clinical PP at End of Therapy	712	741
Clinical PP at Test of Cure	700	713

Sponsor's Table

According to the sponsor, in Study 551, a total of 806 patients were enrolled, 804 of which received study medication and were therefore included in the ITT population. One patient was enrolled but withdrew from the study before receiving study medication, the other patient was lost to follow up at Visit-1. The Bacteriology ITT population comprised the 359 patients in the ITT population (44.7%) who had a least one pathogen identified at screening. In the ITT population, 754 patients (93.8%) completed the study. For the 50 patients who withdrew (6.2%), the most frequent reason for withdrawal was protocol deviation (19 patients, 2.4%).

In Study 592, a total of 861 patients were enrolled, received study medication and were therefore included in the ITT population. The Bacteriology ITT population comprised the 465 patients in the ITT population (54.0%) who had at least one pathogen identified at screening. In the ITT population, 804 patients completed the study. For the 57 patients who withdrew (6.6%), the most frequent reason for withdrawal was adverse experience (18 patients, 2.1%). Eight patients (0.9%) withdrew due to insufficient therapeutic effect.

2.3.2.3 Efficacy Results

Clinical and bacteriological results of principal uncontrolled ABS Studies:

Table 12: Clinical Response at Test of Cure: ABS Principal Uncontrolled Studies 551 and 592 (ITT and Clinical PP Populations)

	Augmentin XR 2000/125mg bid			
Clinical Response	**Study 551**		**Study 592**	
ITT		**N=804**	**N=861**	
Success, n (%)	707	(87.9)	761	(88.4)
Failure, n (%)	97	(12.1)	100	(11.6)
Clinical Failure at End of Therapy, n (%)	25	(3.1)	36	(4.2)
Clinical Recurrence, n (%)	36	(4.5)	36	(4.2)
Unable to Determine, n (%)	36	(4.5)	28	(3.3)
95% CI for Success Rate	**85.4, 90.1**		**86.0, 90.4**	
Clinical PP*		**N=700**	**N=713**	
Success, n (%)	649	(92.7)	676	(94.8)
Failure, n (%)	51	(7.3)	37	(5.2)
95% CI for Success Rate	**90.5, 94.5**		**92.8, 96.3**	

Statistical Reviewer's Comments:

In both studies, the clinical cure rate at the test of cure in the Clinical PP population were; 92.7% in Study 551 and 94.8% in study 592. The rates in the Clinical ITT population were 87.9% in Study 551 and 88.4% in Study 592.

Table 13: Bacteriological Response at Test of Cure: ABS Principal Uncontrolled Studies 551 and 592 (Bacteriology ITT and Bacteriology PP Populations)

	Augmentin XR 2000/125mg Study 551		Augmentin XR 2000/125mg Study 592	
Bacteriology ITT	**N=359**		**N=465**	
Success, n (%)	315	(87.7)	414	(89.0)
Failure, n (%)	44	(12.3)	51	(11.0)
Known Failure, n (%)	26	(7.2)	27	(5.8)
Unable to Determine, n(%)	18	(5.0)	24	(5.2)
95% CI for Success Rate	**83.8, 90.9**		**85.7, 91.7**	
Bacteriology PP	**N=321**		**N=387**	
Success, n (%)	299	(93.1)	373	(96.4)
Failure, n (%)	22	(6.9)	14	(3.6)
95% CI for Success Rate	**89.7, 95.6**		**93.9, 97.9**	

Statistical Reviewer's Comments:

In both studies, the bacteriological eradication (cure) rate at test of cure in the Bacteriology PP population were 93.1% in Study 551 and 96.4% in study 592. The rates in the Bacteriology ITT population were 87.7% in Study 551 and 89.0% in Study 592.

Table 14: Number (%) of Initial Pathogens with Bacteriological Outcome of Eradicated or Presumed Eradicated by Pre-Therapy Pathogen at Test of Cure: ABS Principal Uncontrolled Studies 551 and 592 Combined

(Bacteriology ITT and PP Populations)

	Augmentin XR 2000/125 mg bid Bacteriology ITT		Bacteriology PP**	
	N=824		N=708	
	*n/N**	(%)	*n/N**	(%)
All Pathogens	881/998	(88.3)	811/852	(95.2)
S. pneumoniae	240/257	(93.4)	228/232	(98.3)
H. influenzae	181/207	(87.4)	164/174	(94.3)
M. catarrhalis	70/77	(90.9)	64/65	(98.5)
MSSA	29/35	(82.9)	27/31	(87.1)
K. pneumoniae	32/34	(94.1)	30/31	(96.8)
H. parainfluenzae	23/27	(85.2)	19/19	(100.0)

Data Source: Sponsor's Table

* *n/N* = number of patients with the pathogen eradicated or presumed eradicated / number of patients with the pathogen.

** Data are for the Bacteriology PP population included in the test of cure analyses.

Note: Patients with more than one type of pathogen at screening are counted against each individual micro- organism. Patients with more than one isolate of the same pathogen, are counted only once against the particular pathogen.

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Patients with ABS due to PRSP

The original submission contained 10 patients who were found to have ABS caused by PRSP (PCN MIC≥2.0 ug/ml). The sponsor submitted additional 30 patients with ABS due to PRSP through the open label non-comparative study 592, which makes a total of 40 patients for this NDA.

For ABS, additional analyses was performed after removing the patients enrolled by Dr. Kim Hendrick in addition to the other excluded investigators (Drs. C. Andrew DeAbate, C. P. Mathew and Dr. William N. Sokol). There were 14 patients with PRSP enrolled by Dr. Hendrick, of which 11 patients were from site number 223 and 3 patients were from site 021. There were three patients (551.049.14850, 592.002.21802 and 592.006.22039) with protocol violations. Patient 551.049.14850 had a late EOT visit (20 days), Patient 592.002.21802 had a late TOC visit on day 31 and patient 592.006.22039 had a wrong visit date in the SAS data set and also no PV was reported. Therefore, there were 26 patients in the Bacteriological ITT population and 23 patients in the Bacteriological PP population in the final analysis for ABS excluding the investigator.

Table 15: Clinical and Bacteriological Responses of Augmentin XR for ABS (studies 551 and 592) due to PRSP

	n/M	(%)	95% CI[a]
Bacteriological PP	36/37	(97.3)	(85.8, 99.9)
MIC=2	23/24	(95.8)	(78.9, 99.9)
MIC=4	11/11	(100)	(71.5, 99.9)
MIC=8	1		
MIC=16	1		
Bacteriological ITT	39/40	(97.5)	(86.8, 99.9)
MIC=2	26/27	(96.3)	(81.0, 99.9)
MIC=4	11/11	(100)	(71.5, 99.9)
MIC=8	1		
MIC=16	1		

[a] 95% CIs are calculated using exact probabilities

Statistical Reviewer's Comments:

In the combined (Studies 551 and 592) bacteriological eradication rates for PRSP (penicillin MIC ≥2ug/mL, there were 36/37 (97.3%) cures in the Bacteriological PP population (95% CI: 85.8, 99.9) and of which 23/24 (95.8) had a penicillin MIC of 2ug/ml (95% CI: 78.9, 99.9) and 11/11 had a penicillin MIC of 4ug/ml (95% CI: 71.5,

99.9). The two remaining isolates of MIC 8ug/ml and 16ug/ml were cures. In the Bacteriological ITT population, 39/40 (97.5%) were cures (95% CI: 86.8, 99.9). Among these, 26/27 (96.3%) had a penicillin MIC of 2ug/ml (95% CI:81.0, 99.9) and 11/11 had a penicillin MIC of 4ug/ml (95% CI: 71.5, 99.9).

Table 16: Clinical and Bacteriological Responses of Augmentin XR for ABS (studies 551 and 592) due to PRSP- **Excluding Dr. Kim Hendrick**

	n/M	(%)	95% CI[a]
Bacteriological PP	22/23	(95.7)	(78.1, 99.9)
MIC=2	13/14	(92.9)	(66.1, 99.8)
MIC=4	7/7	(100)	(59.0, 99.9)
MIC=8	1		
MIC=16	1		
Bacteriological ITT	25/26	(96.2)	(80.4, 99.9)
MIC=2	16/17	(94.1)	(71.3, 99.9)
MIC=4	7/7	(100)	(59.0, 99.9)
MIC=8	1		
MIC=16	1		

[a] 95% CIs are calculated using exact probabilities

Statistical Reviewer's Comments:

There were 14 PRSP patients enrolled by Dr. Kim Hendrick. After excluding these patients, there were 22/23(95.7%) cures in the Bacteriological PP population (95% CI: 78.1, 99.9) and of which 13/14 (92.9) had a penicillin MIC of 2ug/ml (95% CI: 66.1, 99.8) and 7/7 had a penicillin MIC of 4ug/ml (95% CI: 59.0, 99.9 In the Bacteriological ITT population, 25/26 (96.2%) were cures (95% CI: 80.4, 99.9). Among these, 16/17 (94.1%) had a penicillin MIC of 2ug/ml (95% CI: 71.3, 99.9) and 7/7 had a penicillin MIC of 4ug/ml (95% CI: 59.0, 99.9).

Table 17: Relationship Between Penicillin MIC and Amoxicillin MIC for PRSP Isolates of ABS Patients

		Penicillin MIC of PRSP Isolate (ug/ml)			
		2.0	4.0	8.0	16.0
Amox MIC	1.0 ug/ml	2	0	0	0
	2.0 ug/ml	18	4	0	0
	4.0 ug/ml	6	4	0	0
	8.0 ug/ml	1	2	1	1
	16.0 ug/ml	0	1	0	0

Statistical Reviewer's Comments:

Based on comparing the penicillin MIC to Amoxicillin MIC, among the patients with Penicillin MIC of 2 ug/ml, 18/27(66.6%) had Amoxicillin MIC of 2ug/ml. Among the patients with Penicillin MIC of 4 ug/ml, only 4/11(36%) had Amoxicillin MIC of 4 ug/ml. There is no adequate evidence for higher MIC's (MIC≥8ug/ml) for amoxicillin,

2.3.2.4 Conclusions and Recommendations

In the principal, open label, uncontrolled studies (Study 551 and Study 592), the primary efficacy variable was the per-patient bacteriological response (success/failure) at test of cure in the Bacteriological PP and ITT populations.

The clinical cure rates at the test of cure for both studies in the Clinical PP population were; 92.7% in Study 551 and 94.8% in study 592. The rates in the Clinical ITT population were 87.9% in Study 551 and 88.4% in Study 592.

The bacteriological eradication(cure) rates at test of cure in the Bacteriology PP population were; 93.1% in Study 551 and 96.4% in study 592. The rates in the Bacteriology ITT population were 87.7% in Study 551 and 89.0% in Study 592.

Among the PRSP cases, the bacteriological eradication rates for PRSP (penicillin MIC ≥2ug/mL), there were 36/37 (97.3%) cures in the Bacteriological PP population (95% CI: 85.8, 99.9). Of which, 23/24 (95.8) had a penicillin MIC of 2ug/ml (95% CI: 78.9, 99.9) and 11/11 had a penicillin MIC of 4ug/ml (95% CI: 71.5, 99.9).

In the Bacteriological ITT population, 39/40 (97.5%) were cures (95% CI: 86.8, 99.9). Among the 39 cures, 26/27 (96.3%) had a penicillin MIC of 2ug/ml (95% CI:81.0, 99.9) and 11/11 had a penicillin MIC of 4ug/ml (95% CI: 71.5, 99.9) excluding the two cases with MIC of 8ug/ml and 16 ug/ml.

Excluding the 14 PRSP patients enrolled by Dr. Kim Hendrick, there were 22/23(95.7%) cures in the Bacteriological PP population (95% CI: 78.1, 99.9). Of which 13/14 (92.9) had a penicillin MIC of 2ug/ml (95% CI: 66.1, 99.8) and 7/7 had a penicillin MIC of 4ug/ml (95% CI: 59.0, 99.9). In the Bacteriological ITT population, 25/26 (96.2%) were cures (95% CI: 80.4, 99.9). Among these patients, 16/17 (94.1%) had a penicillin MIC of 2ug/ml (95% CI: 71.3, 99.9) and 7/7 had a penicillin MIC of 4ug/ml (95% CI: 59.0, 99.9).

Among the patients with Penicillin MIC of 2 ug/ml (Table 17), 18/27(66.6%) had Amoxicillin MIC of 2ug/ml and among the patients with Penicillin MIC of 4 ug/ml, only 4/11(36%) had Amoxicillin MIC of 4 ug/ml. The isolates were all obtained from open label studies (study 551 and study 592).

Overall, based on the data provided, it can be concluded that there is better evidence of efficacy (although not substantial due to few isolates presented) in the treatment of ABS as caused by PRSP with penicillin MIC of 2ug/ml.

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STATISTICAL REVIEW AND EVALUATION

NDA #	:	50-785
Drug	:	Augmentin XR™ (Amoxicillin/Clavulanate potassium)
Sponsor	:	SmithKline Beecham
Indications	:	Community Acquired Pneumonia (CAP), Acute Bacterial Sinusitis (ABS).
Statistical Reviewer	:	Thamban Valappil, Ph.D., HFD-725
Medical Officer	:	Charles Cooper, M.D., HFD-520
Project Manager	:	Susmita Samanta,M.D., HFD-520
Volume Reviewed	:	Vols. 1-112, Item 8: Vols. 1-20
User fee due date	:	December 20, 2001

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I. EXECUTIVE SUMMARY FOR ALL INDICATIONS

INTRODUCTION

Augmentin XR (2000/125mg, 16:1 ratio of amoxicillin/clavulanate) was developed by GlaxoSmithKline Pharmaceuticals specifically for the treatment of Penicillin Resistant Streptococcus Pneumoniae (PRSP) infections involving the respiratory tract. It is a sustained release formulation of which is a combination of the semi-synthetic antibiotic amoxicillin and the beta-lactamase inhibitor clavulanic acid. The concept that lead to the development of this product was the idea that by greatly increasing the amoxicillin content of Augmentin, it may be possible to overcome at least some degree of penicillin resistance. In accordance with this concept, Augmentin XR contains a daily dose of 4,000mg of amoxicillin whereas, the already approved Augmentin formulations (4:1 and 7:1 ratios of amoxicillin to clavulanate) contain only 1,500mg and 1,750mg/daily dose of amoxicllin respectively. This NDA was submitted for the indications: Acute Bacterial Sinusitis (ABS), Community-Acquired Pneumonia (CAP) ——— due to susceptible strains of common pathogens, including beta-lactamase producing strains of H. influenzae and M. catarrhalis. Because the clinical trial program did not yield data to support the indication of PRSP for the treatment of CAP, the current application includes a request only for the treatment of ABS due to PRSP. However, the claim for ABS due to PRSP is not currently being considered by the division because of a divisional policy which requires that efficacy for the treatment of PRSP be demonstrated in CAP prior to other respiratory indications.

Resistant Pathogens

The sponsor's intention for the development of this product was to attain an indication for the treatment of penicillin resistant pneumococcus (PRSP) in the treatment of community acquired pneumonia (CAP) and acute bacterial sinusitis (ABS). It does not currently appear that the sponsor is interested in applying for a PRSP claim for ———

At the time of submission of the NDA, the sponsor's studies had produced only 5 patients with CAP due to PRSP. For this reason, the current NDA has applied only for a standard CAP indication with the ultimate goal being to request a PRSP CAP claim upon the accumulation of sufficient data from ongoing studies.

With regard to the PRSP claim for the treatment of ABS, the division had agreed at the Pre-NDA Meeting that it would allow the pooling of data from AOM 14:1 formulation with PRSP data from the ABS studies conducted for the 16:1 product. The submitted studies included 10 patients with ABS due to PRSP which was combined with 38 cases of AOM due to PRSP. However, the claim for ABS due to PRSP is not currently being considered by the division because of a divisional policy which requires that efficacy for the treatment of PRSP be demonstrated in CAP prior to other respiratory indications.

Therefore, the current application is being evaluated by the division for the potential indications of CAP, ABS, ———

The current NDA is applying for approval for a product (Augmentin XR 16:1) which contains significantly more amoxicillin than the already approved formulation of Augmentin. This is concerning because there are specific safety issues associated with the administration of such large quantities of amoxicillin. No PRSP indication is currently being considered by the division for this product at the present time, and therefore, based on the current data, this product does not offer any specific advantage over the already approved formulations of Augmentin.

The clinical program to evaluate the efficacy of Augmentin XR in the treatment of ABS, CAP [redacted] consists of five randomized, double-blind, controlled clinical studies (Studies 546, 548, 549, 550 and 556). In addition, a single, open, uncontrolled Phase III study for the study of ABS (Study 551) and the interim analysis from a single open, uncontrolled phase III study for the study of CAP (Study 547) are included.

FDA requested a re-analysis of the safety and efficacy of the data by excluding patients enrolled by Drs. C. Mathew DeAbate and C.P. Mathew. These investigators participated in the two Acute Bacterial Sinusitis (ABS) studies (Studies 550 & 551) and the two [redacted] studies (Studies 548 & 549). None of the above investigators participated in the community-acquired pneumonia (CAP) studies submitted in this application. The re-analysis results will be used for the review for all the ABS [redacted] studies.

On May 17, 2001, GSK verbally notified the division that the patients enrolled by Dr. William N. Sokol, was removed from the bacteriological efficacy analysis in study 551, an open label, bacteriologic study in ABS, because Dr. Sokol obtained samples of microbiologic assessment via endoscopy rather than maxillary sinus puncture, as specified in the study protocol. The sponsor has submitted the following studies as listed below by indication.

I. COMMUNITY ACQUIRED PNEUMONIA (CAP) due to:
Streptococcus pneumoniae; *Haemophilus influenzae, Haemophilus parainfluenzae*, methicillin susceptible *Staphylococcus aureus* and *Moraxella catarrhalis* including beta-lactamase producing strains; and *Klebsiella pneumoniae.*

Principal Controlled Studies in CAP

BRL-025000/546 A randomized, double-blind, double-dummy, multicenter parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days versus oral Augmentin 875/125mg twice daily for 7 days in the treatment of bacterial CAP in adults.

BRL-025000/556 A randomized, double-blind, double-dummy, multicenter, parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days versus oral Augmentin 1000/125mg three times daily for 10 days in the treatment of bacterial CAP in adults.

Principal Uncontrolled Study in CAP

BRL-025000/547 An interim analysis of an open, non-comparative, multicenter study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days for the treatment of bacterial CAP in adults.

Review Summary

Study BRL-025000/546: In the Clinical PP test of cure population, the clinical success rate at test of cure was 86.3% in the Augmentin XR group and 91.2% in the Augmentin 875/125 mg group (95% CI: -11.0, 1.2). In the ITT population, the clinical success rate at test of cure was 78.0% in the Augmentin XR group and 82.6% in the Augmentin 875/125 mg group (95% CI: -11.4, 2.3). As the lower limit of the 95% CI for the difference in clinical success rate at test of cure fell below -10% in both PP and ITT populations, it could not be shown from this study that the clinical efficacy of Augmentin XR 2000/125 mg was at least as good as Augmentin 875/125 mg using a non-inferiority margin (delta) of 10% (Table 4). The observed cure rate for Augmentin XR is substantially lower to that of Augmentin 875/125 mg.

In the Bacteriology PP test of cure population, the bacteriological success rates at test of cure were 78.1% in the Augmentin XR group and 84.6% in the Augmentin 875/125 mg group. In the Bacteriology ITT population, the success rates at test of cure were 69.2% in the Augmentin XR group and 83.3% in the Augmentin 875/125 mg group. The 95% CI for the difference in bacteriological cure rates demonstrated that the Augmentin XR 2000/125 mg was not equivalent to Augmentin 875/125 mg using a delta of 10%. It should also be noted that the numbers of patients in the Bacteriology PP and Bacteriology ITT populations were too small to draw any strong and meaningful conclusions.

From a safety perspective, the proportions of patients in both treatment groups experienced AEs which were considered to be of suspected or probable relationship to study medication (Augmentin XR: 25.1%; Augmentin: 24.7%). The most frequently reported AE of suspected or probable relationship to study medication was diarrhoea; (Augmentin XR: 16.9%; Augmentin: 13.1%).

There were three deaths during the study, two in the Augmentin XR group and one in the Augmentin 875/125 mg group, and one further patient in the Augmentin XR group died more than 30 days post-therapy.

Study BRL-025000/556: In the Clinical PP test of cure population, the clinical success rate was 91.5% in the Augmentin XR group and 93.0% in the Augmentin 1g group. Results in the ITT population were 81.1% and 85.7% in the respective treatment groups. In the PP population, the 95% CI (-8.3, 5.4) for the difference in clinical cure rates demonstrated that the Augmentin XR group met the definition of clinical equivalence to the Augmentin 1g group using a delta of 10%. In the ITT population, the clinical efficacy of Augmentin XR was not shown to be at least as good as that of Augmentin 1g, as the lower limit of the 95% CI (-12.5, 3.2) for the difference in cure rates was less than the non-inferiority limit of -10%. The observed cure rate for Augmentin XR is lower to that of Augmentin 1g.

The bacteriological success rate at test of cure in the Bacteriology PP test of cure population was 90.6% in the Augmentin XR group and 84.4% in the Augmentin 1g group. Success rates in the Bacteriology ITT population were 84.1% and 76.6% in the respective treatment groups.

From a safety perspective, during the interval on-therapy plus 30 days post-therapy, a slightly lower proportion of patients in the Augmentin XR group (18.3%) than in the Augmentin 1g group (24.0%) reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication. A higher proportion of patients in the Augmentin XR group (12.4%) reported diarrhoea compared to the proportion of patients in the Augmentin 1g group (8.6%).

Three deaths were reported, two during the interval on-therapy plus 30 days post-therapy and one more than 30 days post-therapy (all in patients treated with Augmentin XR). All were reported as unrelated or unlikely to be related to study treatment.

Based on the 95% CI for the difference in clinical and bacteriological success rate at test of cure and other supporting evidences in both PP and ITT populations, the results were not robust. Therefore, it could not be shown from this study that the clinical efficacy of Augmentin XR is equivalent to that of Augmentin 1g.

Study BRL-025000/547: Based on the interim analysis, the success rate at the test of cure visit in the Bacteriology ITT population was 119/142 (83.8%) and in the Bacteriology PP population was 105/119(88.2%). In the ITT population, the clinical success rate at test of cure was 82.6%. In the Clinical PP test of cure population, the clinical success rate at test of cure was 89.2%. It should be noted that this is an open label, non-comparative trial and drawing any meaningful conclusion of efficacy based on the interim analysis results could be misleading.

In the Bacteriology ITT population at screening, only two patients had isolates of PRSP, one with a penicillin MIC of 2ug/mL and the other with a penicillin MIC of 4ug/mL; they were both also resistant to macrolides, oral tested cephalosporins and trimethoprim/sulfamethoxazole. One PRSP had amoxicillin and amoxicillin/clavulanic acid MICs of 8 ug/mL and the other was susceptible to amoxicillin/clavulanic acid according to the current NCCLS 2000 breakpoint.

During the interval on-therapy plus 30 days post-therapy, 27.9% of patients reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication. The most frequently reported AE with suspected or probable relationship to study medication was diarrhoea (18.1%).

According to the sponsor, the deaths of 8 patients were reported during the interval on-therapy and within 30 days post-therapy. In addition, one patient died after completion of the study and more than 30 days post-therapy. All the adverse experiences resulting in death were reported as unrelated or unlikely to be related to study treatment.

II. [redacted] due to:
Streptococcus pneumoniae and *Haemophilus influenzae, Moraxella catarrhalis, Haemophilus parainfluenzae* and methicillin susceptible *Staphylococcus aureus*, including beta-lactamase producing strains.

Principal Controlled Studies in [redacted]

BRL-025000/548 A randomized, double-blind, double-dummy, multicenter, parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days versus oral clarithromycin 500mg twice daily for 7 days in the treatment of [redacted]

BRL-025000/549 A randomized, double-blind, double-dummy, multicenter, parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days versus oral levofloxacin 500mg once daily for 7 days in the treatment of [redacted]

Review Summary

Study BRL-025000/548: Based on the efficacy re-evaluation by excluding the problematic investigators, in the Clinical PP test of cure population, the clinical success rates at test of cure were 84.6% in the Augmentin XR group and 85.8% in the clarithromycin group with 95% CI (-7.7, 5.3). In the ITT population, the clinical success rates at test of cure were 79.0% in the Augmentin XR group and 81.4% in the clarithromycin group with 95% CI (-8.9, 4.1). In both the populations, the clinical efficacy of Augmentin XR was shown to be at least as good as that of clarithromycin, as the lower limit of the 95% CI for the treatment difference was no less than the non-inferiority margin of -10%.

In the Bacteriology PP, the per patient bacteriological success rates at test of cure were 75.0% in the Augmentin XR group and 78.0% in the clarithromycin 500 group (95% CI: -21.5, 15.4). In the Bacteriology ITT population, the bacteriological success rates at test of cure were 64.3% in the Augmentin XR group and 71.2% in the clarithromycin 500 mg (95% CI: -24.5, 10.7). The 95% CI for the difference in bacteriological response rates demonstrated that the Augmentin XR 2000/125 mg was not equivalent to Clarithromycin 500 mg bid using a delta of 10%. It should also be noted that the numbers of patients in the Bacteriology PP and Bacteriology ITT populations were relatively small to draw any strong and meaningful conclusions.

From a safety perspective, in the Augmentin XR group, during the interval on-therapy plus 30 days post-therapy, 39.3% of patients and 31.8% of patients in the clarithromycin group reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication. A higher proportion of patients in the Augmentin XR group (23.6%) reported diarrhea that was considered to be of suspected or probable relationship to study medication compared to the proportion of patients in the clarithromycin group (9.4%). In addition, 4.8% of Augmentin XR-treated patients reported genital moniliasis that was considered to be of suspected or probable relationship to study medication compared to 0.6% of clarithromycin-treated patients. In the clarithromycin group, 10.1% of patients reported taste perversion as being of suspected or probable relationship to study medication compared to 1.0% of patients in the Augmentin XR group.

Study BRL-025000/549: Based on the efficacy re-evaluation by excluding the problematic investigators, in the Clinical PP test of cure population, the clinical success rate at the test of cure was 85.9% in the Augmentin XR group and 87.1% in the levofloxacin group (95% CI: -7.7, 4.6). In the ITT population, the clinical success rate at test of cure was 79.8% in the Augmentin XR group and 80.6% in the levofloxacin group (95% CI: -7.1, 5.4). The clinical efficacy of Augmentin XR was shown to be at least as good as that of levofloxacin in both populations using a delta of 10%.

Based on the re-evaluation by excluding the problematic investigators, in the Bacteriology PP test of cure population, the bacteriological success rates at test of cure were 80.0% in the Augmentin XR group and 83.1% in the levofloxacin group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 75.6% in the Augmentin XR group and 73.3% in the levofloxacin group. The Bacteriological efficacy of Augmentin XR was not shown to be at least as good as that of levofloxacin in both Bacteriology PP (-16.7, 10.6) and Bacteriology ITT (-11.5, 16.1) populations, using a delta of 10%. It should also be noted that the numbers of patients in the Bacteriology PP and Bacteriology ITT populations were small to draw any strong and meaningful conclusions

Based on sponsor's results, in bacteriologic evaluable patients, one patient in the Augmentin XR group had an isolate of PRSP with a penicillin MIC of 2ug/mL and two patients had isolates of S. pneumoniae which were of intermediate susceptibility to penicillin (MICs of 0.25ug/mL and 1ug/mL). In bacteriologic evaluable patients, a total of 8/51 isolates (15.7%) of H. influenzae, 4/37 isolates (10.8%) of H. parainfluenzae, 24/26 isolates (92.3%) of M. catarrhalis and 12/20 isolates (60.0%) of MSSA were found to produce beta-lactamase.

Diarrhoea was the most frequently reported AE in the Augmentin XR. Among the patients with most frequently reported adverse events, diarrhoea was considered by the investigator to be of suspected or probable relationship to study medication for 39 patients (11.8%) in the Augmentin XR group, compared to 12 patients (3.5%) in the levofloxacin group. Nausea was considered by the investigator to be of suspected or probable relationship to study medication in a similar proportion of patients in each group (Augmentin XR: 2.7%; levofloxacin: 3.5%).

Overall, in both the studies, the role of *streptococcus pneumoniae* with reduced susceptibility to penicillin in — is unclear.

III. ACUTE BACTERIAL SINUSITIS (ABS) due to:
Streptococcus pneumoniae including penicillin-resistant (penicillin MIC ≥2ug/mL) and macrolide-resistant (erythromycin MIC ≥1ug/mL) strains; *Haemophilus influenzae, Moraxella catarrhalis, Haemophilus parainfluenzae* and methicillin susceptible *Staphylococcus aureus* including beta-lactamase producing strains; and *Klebsiella pneumoniae.*

Principal Controlled Study in ABS

BRL-025000/550 *A randomized, double-blind, double-dummy, multicenter parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days versus oral levofloxacin 500mg once daily for 10 days in the treatment of ABS in adults.*

Principal Uncontrolled Study in ABS

BRL-025000/551 An open, non-comparative, multicenter study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days for the treatment of ABS in adults.

To provide further support for the proof of efficacy of Augmentin XR in the treatment of upper respiratory tract infections due to PRSP, data from a non-comparative clinical study (Study 536) which used a 14:1 pediatric suspension (Augmentin ES), are combined with data from ABS Study 551 (as agreed between SB and the Division at the meetings of June 17, 1999 and June 7, 2000). Study 536 investigated the efficacy and safety of Augmentin ES (90/6.4 mg/kg/day) in pediatric patients with acute otitis media (AOM) due to PRSP.

Review Summary

Study BRL-025000/550: Based on the re-evaluation by excluding the problematic investigators, the combined clinical and radiological success rate at test of cure (excluding the problematic investigators) in the Clinical PP population was 83.7% in the Augmentin XR group and 84.3% in the levofloxacin group. Results in the ITT population were 76.4% in the Augmentin XR group

and 83.0% in the levofloxacin group. The combined clinical and radiological response of Augmentin XR was shown to be at least as good as that of levofloxacin in the PP population (95% CI: -9.4, 8.3). Efficacy was not demonstrated in the ITT population (95% CI: -14.9, 1.7) since the lower limit of the 95% CI for the difference in success rates was less than the tolerable limit (-10%).

Although the approval is sought for the treatment of penicillin resistant pneumococcus (PRSP) in the treatment of acute bacterial sinusitis (ABS), there was no adequate number of patients with isolates of PRSP. Hence, this study failed to provide any evidence to support the claim requested.

The most commonly occurring event reported as suspected or probably related to study medication was diarrhoea, and the incidence was higher in the Augmentin XR group (24.1% vs 6.5%). In both treatment groups most of the patients with diarrhoea had the event reported as related to study medication. There were no deaths reported at any time during the study or within 30 days of the end of the study.

Study BRL-025000/551: Based on the reanalysis by excluding the problematic investigators, the per patient bacteriological success rate at test of cure was 87.8% in the Bacteriology ITT population and 93.3 % in the Bacteriology PP test of cure population.. The primary objective of this study was to assess the bacteriological efficacy at the test of cure visit (Days 17-24) of oral Augmentin XR 2000/125mg twice daily (bid) for 10 days in patients with acute bacterial sinusitis (ABS), in particular, infection due to penicillin-resistant *Streptococcus pneumoniae* (PRSP). In the Bacteriology ITT population at screening, only 10 patients had isolates of PRSP.

The clinical response at test of cure in the ITT population was 87.9% after excluding the problematic investigators. In the Clinical PP test of cure population the success rate was 92.7%.

According to the sponsor, out of 10 patients who had isolates of PRSP, 8 of these isolates were also macrolide resistant. Four of the PRSP isolates were resistant to amoxicillin/clavulanic acid with an MIC of 8ug/mL. Nine isolates were also resistant to the oral cephalosporins in this study. The primary efficacy variable for this study was the bacteriological response (success/failure) at test of cure. The results of the primary efficacy analysis show that oral Augmentin XR 2000/125mg twice daily for 10 days has a success rate of 325/370 (87.8%) at test of cure in the Bacteriology ITT population. In the Bacteriology PP test of cure population, with a success rate of 308/330 (93.3%). Of the 10 patients with isolates of PRSP at screening, all had a bacteriological outcome of presumed eradication at test of cure.

Patients with the most frequently reported adverse events with a suspected or probable relationship to the study medication, a total of 224 patients (26.1%) had adverse experiences reported as suspected or probably related to study medication during the interval on-therapy and within 30 days post-therapy. As with adverse experiences overall incidence, the most commonly occurring event reported as suspected or probably related to study medication was diarrhoea, with an incidence of 15.3%. Of the 141 patients with diarrhoea, 131 patients (92.9%) had the event reported as suspected or probably related to study medication.

There were no deaths reported at any time during the study or within 30 days after the end of the study.

The increasing evidence of antibacterial resistance in the pathogens commonly associated with ABS has raised concern about the efficacy of currently available therapies and the sponsor's intention was to obtain an approval for the treatment of penicillin resistant pneumococcus (PRSP) in the treatment of acute bacterial sinusitis (ABS). In the sponsor's analysis, the data from study 536 (38 cases), a study of pediatric patients with Acute Otitis Media (AOM) which uses Augmentin ES (14:1) pediatric suspension has been combined with the data from study 551 Augmentin XR (16:1) to support the efficacy against PRSP. It is not recommended combining the data from these two different studies to get enough PRSP cases. Therefore, apart from the issue of having only one study with PRSP isolates to support the claim, the 10 PRSP patients in study 551 are not adequate to provide enough evidence for a PRSP claim for this indication of ABS.

Overall, for all comparative studies including for CAP and ABS indications, the observed cure rates in Augmentin XR group is lower than that of the comparators.

II. COMMUNITY ACQUIRED PNEUMONIA

In support of this indication, the sponsor has submitted results from two phase III trials. The study titles and objectives of the two trials are as follows. In addition, the sponsor has also provided the results of interim analysis from an on-going study (BRL-025000/547).

Study BRL-025000/546: A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin(XR 2000/125mg Twice Daily Versus Oral Augmentin 875/125mg Twice Daily for 7 Days in the Treatment of Adults with Bacterial Community Acquired Pneumonia.

Study BRL-025000/556: A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin XR 2000/125mg Twice Daily for 10 Days Versus Oral Amoxicillin/Clavulanate 1000/125mg Three Times Daily for 10 Days for the Treatment of Bacterial Community Acquired Pneumonia in Adults.

Study BRL-025000/547-Interim analysis: An Open, ***on-going***, Non-Comparative, Multicentre Study to Assess the Efficacy and Safety of Oral Augmentin XR 2000/125mg Twice Daily for 7 Days for the Treatment of Bacterial Community Acquired Pneumonia in Adults.

STUDY BRL-025000/546

INTRODUCTION

Study Objectives

Primary: To demonstrate that oral Augmentin XR 2000/125mg twice daily for 7 days was at least as effective clinically as oral Augmentin 875/125mg twice daily for 7 days in the treatment of community acquired pneumonia (CAP) in adults.

Secondary: To evaluate the bacteriological efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days and oral Augmentin 875/125mg twice daily for 7 days in the treatment of CAP in adults.

METHODOLOGY

Study Design

This was a randomized, multicentre, double-blind, double-dummy, parallel group, Phase III study to assess the clinical and bacteriological efficacy and safety of oral Augmentin XR in comparison to oral Augmentin 875/125mg for the treatment of CAP. Patients who fulfilled the entry criteria were randomized (1:1) to receive 7 days of treatment with either oral Augmentin XR 2000/125mg twice daily or oral Augmentin 875/125mg twice daily. Patients were to attend the clinic four times: at screening (Visit 1, Day 0), on-therapy (Visit 2, Day 3-5), end of therapy (Visit 3, Day 9-11) and test of cure (Visit 4, Day 28-35).

Study Population

Patients of either gender, aged at least 16 years with a clinical and radiological diagnosis of CAP based on chest radiograph criteria and a number of specific signs and symptoms as defined in the protocol were entered into the study.

Primary Efficacy Variable

- The primary efficacy variable was the clinical response (success or failure) at the test of cure (TOC) at visit 4.

Secondary Efficacy Variables

The secondary efficacy variables were as follows.

- Clinical response (success or failure) at the end of therapy visit (Visit 3)
- Bacteriological response (success or failure) at the test of cure visit (Visit 4)
- Bacteriological response (success or failure) at the end of therapy visit (Visit 3)
- Radiological response (success, failure or unable to determine) at the TOC (Visit 4)
- Radiological response (success, failure or unable to determine) at the end of therapy visit (Visit 3)

Statistical Reviewer's Comments:

The baseline demographic characteristics were summarized to assess the comparability of the treatment groups at baseline. No formal hypothesis testing or interval estimation was applied to baseline or demographic characteristics. Two-sided 95% confidence intervals were calculated for the difference in proportions between the treatment groups using the normal approximation to the binomial distribution.

Testing the equivalence of treatment differences with respect to the efficacy variables were assessed based on a two-tailed 95% confidence interval of the difference in cure rates. The sponsor assumed a high success rate (90%) and a difference between treatment arms not exceeding 10%. The primary efficacy analysis would be evaluated using a non-inferiority margin (delta) of 10% for the 95% confidence interval for the differences in cure rates. The robustness of the primary efficacy analysis will be assessed using the clinically evaluable (PP) and the ITT and/or the Bacteriological ITT (or MITT) populations.

Patient Disposition

The numbers of patients who were randomized to treatment, received at least one dose of study medication and completed the study, and the numbers in each study population are shown in Table 1.

Table 1: Patient Disposition (All Randomized Patients)

	Treatment Group	
	Augmentin XR 2000/125mg bid	Augmentin 875/125mg bid
Population	**n**	**n**
Randomized	255	261
Received Study Medication (ITT/Safety)	255	259
Completed Study	227	228
Clinical PP End of Therapy	221	219
Clinical PP Test of Cure	204	204
Bacteriology ITT	39	30
Bacteriology PP End of Therapy	33	26
Bacteriology PP Test of Cure	32	26

Sponsor's Table

In total, 516 patients were randomized to study treatment; 255 were randomized to receive Augmentin XR and 261 to receive Augmentin 875/125mg. According to the sponsor, there were 514 patients in the ITT population since two patients in the Augmentin group withdrew prior to receiving any study medication and were not included.

Table 2: Number of Patients who were Randomized and Completed the Study, by Country (ITT Population)

	Treatment Group (Sponsor's Table)			
	Augmentin XR 2000/125mg bid N=255		Augmentin 875/125mg bid N=259	
Country	**R**	**C**	**R**	**C**
Belgium	7	6	6	6
Germany	73	70	81	78
Mexico/Guatemala *	13	10	11	10
USA	162	141	161	134
Total	255	227	259	228

Sponsor's Table : R = randomized; C = completed.

* Patients from centre 700 in Guatemala (Augmentin XR: 5 patients; Augmentin: 4 patients) were combined with patients from the centres in Mexico (centre 600 (Augmentin XR: 1 patient; Augmentin: 0 patients), centre 601 (Augmentin XR: 2 patients; Augmentin: 2 patients) and centre 603 (Augmentin XR: 5 patients; Augmentin: 5 patients)).

Demographic and Baseline Characteristics

The demographic characteristics in the two treatment groups of the ITT population is summarized in Table 3.

Table 3: Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group: Augmentin XR 2000/125mg bid N=255		Augmentin 875/125mg bid N=259	
Gender n (%)				
Male	130	(51.0)	127	(49.0)
Female	125	(49.0)	132	(51.0)
Age (year)				
Mean (SD)	52.0 (17.8)		52.5 (17.6)	
Range	17 – 90		16 - 91	
Race n (%)				
White	211	(82.7)	223	(86.1)
Black	20	(7.8)	14	(5.4)
Oriental	3	(1.2)	1	(0.4)
Other*	21	(8.2)	21	(8.1)
Weight (kg)				
Mean (SD)	79.2 (21.4)		79.8 (21.7)	
Range	31.0 – 170.0		28.0 - 170.9	
Height (cm)				
Mean (SD)	169.5 (10.6)**		169.3 (9.9)	
Range	131.0 – 205.7		128.0 - 198.1	
Smoking History n (%)				
Current Smoker	82	(32.2)	79	(30.5)
Ever Smoked	141	(55.3)	149	(57.5)
Smoking Pack Years:				
0	114	(44.7)	111	(42.9)
>0 – 10	48	(18.8)	57	(22.0)
>10 – 20	24	(9.4)	31	(12.0)
>20 – 30	27	(10.6)	18	(6.9)
>30	40	(15.7)	39	(15.1)
Unknown	2	(0.8)	3	(1.2)
In-Patient n (%)	12	(4.7)	12	(4.6)

* The other races, as recorded verbatim by the investigator were for the Augmentin XR group: Hispanic, 19 patients; Portuguese, 1 patient; Asian, 1 patient, and for the Augmentin group: Hispanic 19 patients; Portuguese, 1 patient; Native American, 1 patient.

** n=254 for the Augmentin XR group (height was missing for one patient).

Statistical Reviewer's Comments:

In the ITT test of cure populations, no major differences were evident between the two treatment groups with respect to demographic characteristics. For the ITT population, the mean age was 52.0 years in the Augmentin XR group and 52.5 years in the Augmentin 875/125mg *group. In both treatment groups approximately half of the patients were male (Augmentin XR: 51.0%; Augmentin* 875/125mg*: 49.0%) and the majority of patients were white (Augmentin XR: 82.7%; Augmentin* 875/125mg*: 86.1%).*

RESULTS

EFFICACY

Four patient populations (ITT, Bacteriology ITT, Clinical PP and Bacteriology PP) were identified for the analysis of efficacy.

In this review, the results for the PP populations (Clinical PP for clinical endpoints and Bacteriology PP for bacteriological endpoints) are presented along with results for the ITT and Bacteriological ITT populations.

Table 4: Clinical Response at Test of Cure (Clinical PP Test of Cure and ITT Populations)

	Treatment Group			
Clinical Response	**Augmentin XR 2000/125mg bid**		**Augmentin 875/125mg bid**	
Clinical PP Test of Cure Population	**N=204**		**N=204**	
Success n (%)	176	(86.3)	186	(91.2)
Failure n (%)	28	(13.7)	18	(8.8)
Clinical Failure at End of Therapy	21	(10.3)	12	(5.9)
Clinical Recurrence at Test of Cure	7	(3.4)	6	(2.9)
Treatment Difference % (Augmentin XR – Augmentin)	-4.9			
95% CI	-11.0, 1.2			
ITT Population	**N=255**		**N=259**	
Success n (%)	199	(78.0)	214	(82.6)
Failure n (%)	56	(22.0)	45	(17.4)
Clinical Failure at End of Therapy	26	(10.2)	20	(7.7)
Clinical Recurrence at Test of Cure	8	(3.1)	7	(2.7)
Unable to Determine	22	(8.6)	18	(6.9)
Treatment Difference % (Augmentin XR – Augmentin)	-4.6			
95% CI	-11.4, 2.3			

Statistical Reviewer's Comments:

In the Clinical PP test of cure population, the clinical success rate at test of cure was 86.3% in the Augmentin XR group and 91.2% in the Augmentin group. In the ITT population, the clinical success rate at test of cure was 78.0% in the Augmentin XR group and 82.6% in the Augmentin group. As the lower limit of the 95% CI for the difference in clinical success rate at test of cure fell below -10% in both PP and ITT populations, it could not be shown from this study that the clinical efficacy of Augmentin XR 2000/125 mg was at least as good as Augmentin 875/125 mg using a non-inferiority margin (delta) of 10% (Table 4).

Table 5: Number (%) of Patients with Common Typical Pathogens Associated with CAP at Screening from Sputum, Respiratory Sample or Blood (Bacteriology ITT and Bacteriology PP Test of Cure Populations)

	Treatment Group			
	Augmentin XR 2000/125mg bid		Augmentin 875/125mg bid	
Pre-Therapy Pathogen	**n**	**(%)**	**n**	**(%)**
Bacteriology ITT Population	**N=39**		**N=30**	
S. pneumoniae	10	(25.6)	6	(20.0)
H. influenzae	8	(20.5)	8	(26.7)
H. parainfluenzae	5	(12.8)	8	(26.7)
MSSA*	5	(12.8)	2	(6.7)
M. catarrhalis	4	(10.3)	2	(6.7)
Bacteriology PP Test of Cure Population	**N=32**		**N=26**	
S. pneumoniae	9	(28.1)	6	(23.1)
H. influenzae	6	(18.8)	7	(26.9)
H. parainfluenzae	5	(15.6)	7	(26.9)
MSSA*	4	(12.5)	1	(3.8)
M. catarrhalis	2	(6.3)	1	(3.8)

Sponsor's Table

* MSSA = methicillin-susceptible *S. aureus*.

Notes: One patient in the Augmentin XR group had a methicillin-resistant *S. aureus* (MRSA). Some patients may have had more than one pathogen.

Statistical Reviewer's Comments:

According to sponsor, overall in the Bacteriology ITT population at screening, 17.6% (3 isolates) of S. pneumoniae *were resistant to penicillin and 17.6% (3 isolates) were resistant to macrolides (erythromycin MIC ≥1ug/ml). The three PRSP isolates, one of which was also resistant to macrolides, and two other macrolide resistant* S. pneumoniae *isolates.*

Table 6: Initial Typical Pathogen Bacteriological Outcome at Test of Cure (For All Typical Pathogens Combined and the Most Frequent Typical Pathogens) (Bacteriology PP Test of Cure Population)

		Treatment Group			
		Augmentin XR 2000/125mg bid N=32		Augmentin 875/125mg bid N=26	
Initial Pathogen	Bacteriological Outcome	n	(%)	n	(%)
All Pathogens					
	Eradication	1	(2.8)	1	(3.1)
	Presumed Eradication	27	(75.0)	25	(78.1)
	Failure	1	(2.8)	3	(9.4)
	Presumed Failure	7	(19.4)	3	(9.4)
S. pneumoniae					
	Presumed Eradication	7	(77.8)	5	(83.3)
	Presumed Failure	2	(22.2)	1	(16.7)
H. influenzae					
	Eradication	1	(16.7)	0	
	Presumed Eradication	4	(66.7)	5	(71.4)
	Failure	0		1	(14.3)
	Presumed Failure	1	(16.7)	1	(14.3)
H. parainfluenzae					
	Eradication	0		1	(14.3)
	Presumed Eradication	4	(80.0)	6	(85.7)
	Presumed Failure	1	(20.0)	0	

Sponsor's Table

n (%) = number (%) of pathogens with a particular outcome;

Note The failure category includes pathogens which persisted at end of therapy or recurred at test of cure. The presumed failure category includes pathogens which were presumed to have persisted at end of therapy or presumed to have recurred at test of cure.

Statistical Reviewer's Comments:

In the Bacteriology PP test of cure population, the initial isolates either eradicated or presumed eradicated at test of cure were; (Augmentin XR: 28/36 isolates, 77.8%; Augmentin: 26/32 isolates, 81.3%). Results for individual pathogens account for only small number of isolates.

The bacteriological outcomes in this table are not mutually exclusive.

Table 7: Per Patient Bacteriological Response at Test of Cure (Bacteriology PP Test of Cure and Bacteriology ITT Populations)

Bacteriological Response	Treatment Group: Augmentin XR 2000/125mg bid		Augmentin 875/125mg bid	
Bacteriology PP Test of Cure Population	**N=32**		**N=26**	
Success n (%)	25	(78.1)	22	(84.6)
Failure n (%)	7	(21.9)	4	(15.4)
Treatment Difference % (Augmentin XR – Augmentin)	-6.5			
95% CI	-26.4, 13.4			
Bacteriology ITT Population	**N=39**		**N=30**	
Success n (%)	27	(69.2)	25	(83.3)
Failure* n (%)	12	(30.8)	5	(16.7)
Treatment Difference % (Augmentin XR – Augmentin)	-14.1			
95% CI	-33.8, 5.6			

* Includes 3 patients in the Augmentin XR group with a bacteriological outcome of unable to determine; no patients in the Augmentin group had a bacteriological outcome of unable to determine.

Statistical Reviewer's Comments:

In the Bacteriology PP test of cure population, the bacteriological success rates at test of cure were 78.1% in the Augmentin XR group and 84.6% in the Augmentin group. In the Bacteriology ITT population, the success rates at test of cure were 69.2% in the Augmentin XR group and 83.3% in the Augmentin group. The 95% CI for the difference in bacteriological cure rates demonstrated that the Augmentin XR 2000/125 mg was not equivalent to Augmentin 875/125 mg using a delta of 10%. It should also be noted that the numbers of patients in the Bacteriology PP and Bacteriology ITT populations were too small to draw any strong and meaningful conclusions.

Table 8: Radiological Response at Test of Cure (Clinical PP Test of Cure and ITT Populations)

	Treatment Group			
Radiological Response	**Augmentin XR 2000/125mg bid**		**Augmentin 875/125mg bid**	
Clinical PP Test of Cure Population	**N=204**		**N=204**	
Success n (%)	173	(84.8)	184	(90.2)
Failure n (%)	8	(3.9)	7	(3.4)
Unable to Determine n (%)	23	(11.3)	13	(6.4)
Treatment Difference % (Augmentin XR – Augmentin)	-5.4			
95% CI	-11.8, 1.0			
ITT Population	**N=255**		**N=259**	
Success n (%)	193	(75.7)	209	(80.7)
Failure n (%)	11	(4.3)	9	(3.5)
Unable to Determine n (%)	51	(20.0)	41	(15.8)
Treatment Difference % (Augmentin XR – Augmentin)	-5.0			
95% CI	-12.1, 2.1			

Statistical Reviewer's Comments:

In the Clinical PP test of cure population, the radiological success rate at test of cure was 84.8% in the Augmentin XR group and 90.2% in the Augmentin group. In the ITT population, the radiological success rate at test of cure was 75.7% in the Augmentin XR group and 80.7% in the Augmentin group. The 95% CI for the difference in bacteriological cure rates failed to demonstrate that the Augmentin XR 2000/125 mg was equivalent to Augmentin 875/125 mg using a delta of 10% (Table 8).

SAFETY

All randomized patients who received at least one dose of study medication (ie the ITT population) were included in the analysis of safety.

Table 9: Number (%) of Patients with the Most Frequently Reported Adverse Experiences (≥2% of Patients)

	Treatment Group			
	Augmentin -R 2000/125mg bid N=255		Augmentin 875/125mg bid N=259	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at Least One AE	126	(49.4)	133	(51.4)
Diarrhoea	46	(18.0)	37	(14.3)
Nausea	11	(4.3)	14	(5.4)
Headache	11	(4.3)	13*	(5.0)
Rhinitis	7	(2.7)	5	(1.9)
Sinusitis	6	(2.4)	5	(1.9)
Vomiting	4	(1.6)	7	(2.7)
Abdominal Pain	4	(1.6)	6	(2.3)

Sponsor's Table

* This number includes one Augmentin-treated patient (546.118.00363) who had a baseline AE of headache included in the on-therapy time imterval in error.

Statistical Reviewer's Comments:

Based on sponsor's results, during the interval on-therapy and within 30 days post-therapy, the incidence of patients reporting with at least one AE was; (Augmentin –R: 49.4%; Augmentin: 51.4%).

Adverse Experiences by Relationship to Study Medication

The number (%) of patients with the most frequently reported AEs (ie, those occurring in at least 1% of patients in either treatment group) of suspected or probable relationship to study medication during the interval on-therapy and within 30 days post-therapy are summarized in Table 10.

Table 10: Number (%) of Patients with the Most Frequently Reported Adverse Experiences with a Suspected or Probable Relationship to Study Medication (≥1% of Patients)

	Treatment Group			
	Augmentin XR 2000/125mg bid N=255		Augmentin 875/125mg bid N=259	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at Least One AE with Suspected or Probable Relationship	64	(25.1)	64	(24.7)
Diarrhoea	43	(16.9)	34	(13.1)
Nausea	7	(2.7)	12	(4.6)
Genital Moniliasis	3	(1.2)	3	(1.2)
Gastrointestinal Disorder NOS*	3	(1.2)	2	(0.8)
Genital Pruritus	3	(1.2)	1	(0.4)
Abdominal Pain	2	(0.8)	4	(1.5)
Vomiting	1	(0.4)	3	(1.2)

*NOS= Not Otherwise Specified
Sponsor's Table

Statistical Reviewer's Comments:

The proportions of patients in both treatment groups experienced AEs which were considered to be of suspected or probable relationship to study medication (Augmentin XR: 25.1%; Augmentin: 24.7%) are given in Table 10 above. The most frequently reported AE of suspected or probable relationship to study medication was diarrhoea; (Augmentin XR: 16.9%; Augmentin: 13.1%).

Deaths

There were three deaths during the study, two in the Augmentin XR group and one in the Augmentin group, and one further patient in the Augmentin XR group died more than 30 days post-therapy.

Adverse Experiences by Severity

The number (%) of patients with at least one AE, by severity, during the interval on-therapy and within 30 days post-therapy are summarized in Table 11.

Table 11: Number (%) of Patients with the Most Frequently Reported Adverse Experiences by Time of First Occurrence

		Time Interval**							
		Day 0-5		Day 6-13		Day 14-20		Day 21+	
Adverse Experience	**N***	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Augmentin XR 2000/125mg bid									
Patients with at Least One AE†	**127**	**84**	**(32.9)**	**46**	**(18.0)**	**16**	**(6.3)**	**31**	**(12.2)**
Preferred Term††									
Diarrhoea	**46**	42	(91.3)	3	(6.5)	0		1	(2.2)
Headache	**11**	5	(45.5)	2	(18.2)	2	(18.2)	2	(18.2)
Nausea	**11**	7	(63.6)	1	(9.1)	0		3	(27.3)
Rhinitis	**8**	0		3	(37.5)	2	(25.0)	3	(37.5)
Sinusitis	**6**	0		1	(16.7)	2	(33.3)	3	(50.0)
Augmentin 875/125mg bid									
Patients with at Least One AE†	**133**	**92**	**(35.5)**	**47**	**(18.1)**	**13**	**(5.0)**	**23**	**(8.9)**
Preferred Term††									
Diarrhoea	**37**	35	(94.6)	2	(5.4)	0		0	
Nausea	**14**	12	(85.7)	2	(14.3)	0		0	
Headache	**13#**	7	(53.8)	5	(38.5)	0		1	(7.7)
Vomiting	**7**	7	(100.0)	0		0		0	
Abdominal Pain	**6**	3	(50.0)	1	(16.7)	0		2	(33.3)

Sponsor's Table

* N = number of patients with at least one adverse experience, or a particular adverse experience.

** Included adverse experiences occurring on-therapy and at any time post-therapy.

† n (%) = number (%) of patients with at least one adverse experience in a particular interval, expressed as a percentage of the total number of patients in the treatment group (Augmentin XR: 255; Augmentin : 259).

†† n (%) = number (%) of patients with the adverse experience in a particular interval, expressed as a percentage of the total number of patients with the adverse experience overall.

\# This number includes one Augmentin-treated patient (546.118.00363) who had a baseline AE of headache included in the on-therapy time imterval in error.

Statistical Reviewer's Comments:

Based on table 11, in both treatment groups, the proportions of patients experiencing an AE for the first time were; Augmentin XR 2000/125 mg bid: 32.9% and Augmentin 875/125 mg bid: 32.5 and for Day 21+ Augmentin XR group had higher rate of adverse events (12.2%, n=31) compared to Augmentin 875/125 mg bid (8.9%, n=23). Of those patients with diarrhoea or nausea, the majority reported the event for the first time during the Day 0-5 interval (diarrhoea - Augmentin XR: 91.3%; Augmentin: 94.6%; nausea - Augmentin XR: 63.6%; Augmentin: 85.7%).