pathogens were each isolated from 16 patients in the Bacteriology ITT population, and in Study 556, *S. pneumoniae* was isolated from 45 patients (49.5%) and *H. influenzae* from 24 patients (26.4%) in total. The majority of patients from whom *S. pneumoniae* and *H. influenzae* were isolated presented with single pathogen infections.

Few patients in both studies were bacteremic at screening. In Study 546, only four patients in the Augmentin XR group and two patients in the Augmentin 875/125mg group had a typical pathogen isolated from blood at screening in the Bacteriology ITT population. The pathogens cultured from the blood of the four patients in the Augmentin XR group were *S. pneumoniae, Acinetobacter lwoffi, Haemophilus aphrophilus* and *Pasteurella multocida*. For the two patients in the Augmentin 875/125mg group, MSSA and viridans group streptococci were isolated from one patient and viridans group streptococci only was isolated from the second patient. All six of the bacteremic patients were included in the Clinical PP population at end of therapy and test of cure. In Study 556, three patients in the Augmentin XR group and 8 patients in the Augmentin 1000/125mg group had a typical pathogen isolated from blood at screening in the Bacteriology ITT population. No patients in either treatment group had more than one pathogen identified in their blood. In this study, the most prevalent pathogen isolated from blood culture was *S. pneumoniae* isolated from three patients in the Augmentin XR group and 6 patients in the Augmentin 1000/125mg group in the Bacteriology ITT population. For a small number of patients in each study the bacteremic status was unknown (16 patients in Study 546 and 10 patients in Study 556, Bacteriology ITT populations).

A summary of the number of patients with key pathogens associated with CAP at screening in each of the principal studies is presented in the following table.

Number (%) of Patients with Key Typical Pathogens Associated with CAP at Screening from any Source: CAP Principal Controlled Studies 546 and 556 (Bacteriology PP and ITT Test of Cure Population)

Pathogen	Study 546				Study 556			
	Augmentin XR 2000/125mg b.i.d.		Augmentin 875/125mg b.i.d.		Augmentin XR 2000/125mg b.i.d.		Augmentin 1000/125mg tid	
	n	(%)	n	(%)	n	(%)	n	(%)
Bacteriology PP	N=32		N=26		N=32		N=32	
Total *S. pneumoniae*	9	(28.1)	6	(23.1)	17	(53.1)	18	(56.3)
Single pathogen *S. pneumoniae*	8	(25.0)	3	(11.5)	13	(40.6)	10	(31.3)
Total *H. influenzae*	6	(18.8)	7	(26.9)	5	(15.6)	10	(31.3)
Single pathogen *H. influenzae*	4	(12.5)	5	(19.2)	5	(15.6)	6	(18.8)
Total *M. catarrhalis*	2	(6.3)	1	(3.8)	3	(9.4)	1	(3.1)
Single pathogen *M. catarrhalis*	1	(3.1)	0		3	(9.4)	0	
Total *K. pneumoniae*	0		1	(3.8)	3	(9.4)	1	(3.1)
Single pathogen *K. pneumoniae*	0		1	(3.8)	2	(6.3)	1	(3.1)
Total *H. parainfluenzae*	5	(15.6)	7	(26.9)	2	(6.3)	2	(6.3)
Single pathogen *H. parainfluenzae*	2	(6.3)	4	(15.4)	0		0	
Total MSSA	4	(12.5)	1	(3.8)	2	(6.3)	1	(3.1)
Single pathogen MSSA	2	(6.3)	0		0		1	(3.1)
Bacteriology ITT	N=39		N=30		N=44		N=47	
Total *S. pneumoniae*	10	(25.6)	6	(20.0)	23	(52.3)	22	(46.8)
Single pathogen *S. pneumoniae*	8	(20.5)	3	(10.0)	17	(38.6)	12	(25.5)
Total *H. influenzae*	8	(20.5)	8	(26.7)	9	(20.5)	15	(31.9)
Single pathogen *H. influenzae*	4	(10.3)	5	(16.7)	8	(18.2)	10	(21.3)
Total *M. catarrhalis*	4	(10.3)	2	(6.7)	3	(6.8)	2	(4.3)
Single pathogen *M. catarrhalis*	2	(5.1)	0		3	(6.8)	1	(2.1)
Total *K. pneumoniae*	1	(2.6)	1	(3.3)	3	(6.8)	1	(2.1)
Single pathogen *K. pneumoniae*	0		1	(3.3)	2	(4.5)	1	(2.1)
Total *H. parainfluenzae*	5	(12.8)	8	(26.7)	2	(4.5)	3	(6.4)
Single pathogen *H. parainfluenzae*	2	(5.1)	5	(16.7)	0		0	
Total MSSA	5	(12.8)	2	(6.7)	2	(4.5)	3	(6.4)
Single pathogen MSSA	2	(5.1)	1	(3.3)	0		2	(4.3)

Note: some patients may have had more than one pathogen at screening.

The Bacteriology ITT population in both studies consisted of patients with a typical pathogen only, as well as patients with a typical pathogen who were also seropositive for an atypical pathogen at screening. Among patients with typical pathogens in Study 546, 10 patients in the Augmentin XR group and 7 patients in the Augmentin 875/125mg group were also seropositive for atypical pathogens in the Bacteriology ITT population (note: some patients had >1 atypical pathogen). In the Bacteriology ITT population of Study 556, a slightly higher proportion of patients in the Augmentin 1000/125mg group (15/47, 31.9%) were seropositive for atypical pathogens at screening compared with the Augmentin XR group (8/44, 18.2%). The only atypical pathogens identified by serology in the Bacteriology ITT populations in both studies were *M. pneumoniae* and *C. pneumoniae*. None of these patients were seropositive for either *L. pneumophila* or *C. psittaci*.

In addition to these patients in the Bacteriology ITT population, there were patients who were seropositive for atypical pathogens but had no positive cultures at screening for typical pathogens and were therefore excluded from the Bacteriology ITT population. In Study 546, 52 patients in the Augmentin XR group were in this category of whom 39 were seropositive for *M. pneumoniae* and 19 were seropositive for *C. pneumoniae*; in the Augmentin 875/125mg group, 58 patients were in this category of whom 44 were seropositive for *M. pneumoniae*, 17 were seropositive for *C. pneumoniae* and 1 was seropositive for *L. pneumophila*. In Study 556, 31 patients in the Augmentin XR group and 33 patients in the Augmentin 1000/125mg group of the ITT population were seropositive for an atypical pathogen only. In these patients the most common atypical pathogen was again *M. pneumoniae* for which 18/31 patients in the Augmentin XR group and 20/33 patients in the Augmentin 1000/125mg group were seropositive.

A summary of patients who were seropositive for atypical pathogens in the Bacteriology ITT and PP populations is presented in the following table.

Number (%) of Patients Seropositive for Atypical Pathogens at Screening: CAP Principal Controlled Studies 546 and 556 (Bacteriology PP Test of Cure and Bacteriology ITT Populations)

	Study 546				Study 556			
	Augmentin XR 2000/125mg b.i.d.		Augmentin 875/125mg b.i.d.		Augmentin XR 2000/125mg b.i.d.		Augmentin 1000/125mg tid	
	n	(%)	n	(%)	n	(%)	n	(%)
Bacteriology PP	N=32		N=26		N=32		N=32	
M. pneumoniae	7	(21.9)	5	(19.2)	4	(12.5)	4	(12.5)
*C. pneumoniae**	3	(9.4)	2	(7.7)	3	(9.4)	5	(15.6)
Bacteriology ITT	N=39		N=30		N=44		N=47	
M. pneumoniae	9	(23.1)	5	(16.7)	5	(11.4)	9	(19.1)
*C. pneumoniae**	4	(10.3)	2	(6.7)	3	(6.8)	6	(12.8)

* Definitive diagnosis based on a single *C. pneumoniae* IgG titer of ≥1:16 and IgM ≥1:10 and IgA ≥1:16.

The susceptibility (in terms of MIC and % susceptible, intermediate and resistant) of the key pathogens *S. pneumoniae* and *H. influenzae* (also *H. parainfluenzae* in Study 546) was determined against a panel of antibacterial agents. *Haemophilus spp, M. catarrhalis, Enterococcus spp*, and *S. aureus* were tested for beta-lactamase production. In both studies, ≥90% of isolates of these pathogens were susceptible to amoxicillin/clavulanic acid based on the breakpoint defined by the NCCLS, 2000.

In Study 546 in the Bacteriology ITT population at screening, three isolates of *S. pneumoniae* (17.6%) were resistant to penicillin (penicillin MIC ≥2μg/mL); two were isolated from patients in the Augmentin XR group (one was also macrolide-resistant) and one was isolated from a patient in the Augmentin 875/125 mg group. An additional two patients (one in each treatment group) had isolates that were resistant to macrolides (erythromycin MIC ≥1μg/ml). In addition, 2/16 *H. influenzae* isolates, 1/13 *H. parainfluenzae* isolates, 7/7 MSSA isolates and 5/6 *M. catarrhalis* isolates produced beta-lactamase (Table 33).

In Study 556, three *S. pneumoniae* isolates (8.3%) were resistant to penicillin at screening (one was isolated from an Augmentin XR patient and two were from Augmentin 1000/125mg patients). All three PRSP isolates were also macrolide-resistant.

An additional three *S. pneumoniae* isolates were macrolide-resistant. Overall, in the Bacteriology ITT population at screening, 4/24 (16.7%) *H. influenzae* isolates, 2/5 *H. parainfluenzae* isolates, 5/5 *M. catarrhalis* isolates, and 3/5 MSSA isolates produced beta-lactamase.

A summary of the number of patients with key resistant pathogens in each of the principal studies is presented in the following table.

Number (%) Patients with Resistant Pathogens at Screening: CAP Principal Controlled Studies 546 and 556 (Bacteriology ITT Population)

	Study 546				Study 556			
	Augmentin XR 2000/125mg b.i.d.		Augmentin 875/125mg b.i.d.		Augmentin XR 2000/125mg b.i.d.		Augmentin 1000/125mg t.i.d.	
Bacteriology ITT	N=39		N=30		N=44		N=47	
	n/N	(%)	*n/N*	(%)	*n/N*	(%)	*n/N*	(%)
Penicillin-resistant *S. pneumoniae*	2/11	(18.2)	1/6	(16.7)	1/24	(4.2)	2/24	(8.3)
Erythromycin Resistant *S. pneumoniae*	2/11	(18.2)	1/6	(16.7)	3/24	(12.5)	3/24	(12.5)
Beta-Lactamase (+) *H. influenzae*	0/8	-	2/8	(25.0)	3/9	(33.3)	1/15	(6.7)
Beta-Lactamase (+) *H. parainfluenzae*	0/5	-	1/8	(12.5)	1/2	(50.0)	1/3	(33.3)
Beta-Lactamase (+) *M. catarrhalis*	3/4	(75.0)	2/2	(100.0)	3/3	(100.0)	2/2	(100.0)
Beta-Lactamase (+) MSSA	5/5	(100.0)	2/2	(100.0)	1/2	(50.0)	2/3	(66.7)

Efficacy Results of Principal Controlled CAP Studies

Primary Efficacy Variable

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

At test of cure in the Clinical PP population of Study 546, a high clinical success rate was achieved with both Augmentin regimens (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 however, 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 just outside the pre-defined limit of -10% to demonstrate non-inferiority.

Clinical success rates for Study 546 were similar to those from other studies of Augmentin in which follow-up response rates for evaluable patients ranged from 75-89%. However, in Study 546, the criterion to demonstrate the non-inferiority limit of Augmentin XR compared with Augmentin 875/125mg was not achieved. An analysis of the primary efficacy variable by country group (US, non-US), indicated that in US patients the non-inferiority criterion of –10% was achieved (95% CI: -9.9, 7.4 for Clinical PP analysis; 95% CI: -9.8, 8.8 for ITT analysis). However, in non-US patients the clinical success rate was significantly higher in the comparator group compared with patients who received Augmentin XR, even though the clinical success rate for Augmentin XR was similar in US and non-US patients.

MO COMMENT: The success rate of the active control comparator group was significantly higher amongst non-U.S. patients. Upon review, there is no clear explanation for this, however, the difference was largely the result of a very high efficacy rate amongst active control patients enrolled in the German centers. These consisted mostly of multiple centers with small numbers of enrolled patients and no explanation could be discerned from review of the data.

The results of principal Study 556 demonstrate that 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. In each population, the lower limit of the 95% CI for the treatment difference (Augmentin XR – Augmentin 1000/125mg) was no less than the pre-defined non-inferiority limit for this study of -15%, (-8.3, 5.4) for Clinical PP analysis and (-12.5, 3.2) for the ITT analysis.

The results of the primary analysis for each study are presented in the following table.

Clinical Response at Test of Cure: CAP Principal Controlled Studies 546 and 556 (Clinical PP and ITT Populations)

Population	Study 546 Augmentin XR 2000/125mg b.i.d. (7 days)		Study 546 Augmentin 875/125mg b.i.d. (7 days)		Study 556 Augmentin XR 2000/125mg b.i.d. (10 days)		Study 556 Augmentin 1000/125mg tid (10 days)	
Clinical PP								
N	204		204		118		114	
Success, n (%)	176	(86.3)	186	(91.2)	108	(91.5)	106	(93.0)
Failure, n (%)	28	(13.7)	18	(8.8)	10	(8.5)	8	(7.0)
Clinical Failure at End of Therapy, n (%)	21	(10.3)	12	(5.9)	9	(7.6)	8	(7.0)
Clinical Recurrence, n (%)	7	(3.4)	6	(2.9)	1	(0.8)	0	
Treatment Difference, %	-4.9				-1.5			
95% CI	-11.0, 1.2				-8.3, 5.4			
ITT								
N	255		259		169		175	
Success, n (%)	199	(78.0)	214	(82.6)	137	(81.1)	150	(85.7)
Failure, n (%)	56	(22.0)	45	(17.4)	32	(18.9)	25	(14.3)
Clinical Failure at End of Therapy, n (%)	26	(10.2)	20	(7.7)	16	(9.5)	12	(6.9)
Clinical Recurrence, n (%)	8	(3.1)	7	(2.7)	3	(1.8)	0	
Unable to Determine, n (%)	22	(8.6)	18	(6.9)	13	(7.7)	13	(7.4)
Treatment Difference, %	-4.6				-4.6			
95% CI	-11.4, 2.3				-12.5, 3.2			

Treatment Effect Across Countries

In both CAP studies, the primary efficacy analysis was assessed by logistic regression, using country as a categorical covariate, to determine whether the treatment effect was consistent across participating countries. The country by treatment interaction was not significant in either study. (for Study 556, countries were grouped as planned into 'France' or 'Non-France' for all remaining countries) However, in Study 546, the majority of patients were enrolled in the US and, therefore, a retrospective analysis was carried out to investigate a possible country-group (US, non-US) by treatment interaction. In this analysis a significant treatment by country interaction was observed.

The results of the analysis of clinical response at test of cure by country group (US, non-US), indicated that in US patients the non-inferiority criterion of –10% was achieved; in non-US patients a statistically significant difference in favor of Augmentin 875/125mg b.i.d. was observed.

In the US group, the clinical success rate at test of cure was similar in both treatment groups for the Clinical PP and ITT populations and was consistent with the overall clinical success rate for Augmentin XR-treated patients in the analysis of the primary efficacy variable. Similar clinical success rates to the US rates were also noted in the Augmentin XR group when non-US countries were combined, however, the success rate in the Augmentin 875/125mg group was much higher for the non-US countries.

Clinical Success Rate at Test of Cure, US versus Non-US (Clinical PP and ITT Populations)

Clinical PP	ITT

	Augmentin XR 2000/125mg b.i.d.		Augmentin 875/125mg b.i.d.		Augmentin XR 2000/125mg b.i.d.		Augmentin 875/125mg b.i.d.	
US	n	(%)	n	(%)	n	(%)	n	(%)
N	121		117		162		161	
Success, n (%)	104	(86.0)	102	(87.2)	123	(75.9)	123	(76.4)
Failure, n (%)	17	(14.0)	15	(12.8)	39	(24.1)	38	(23.6)
Treatment Difference, %*	-1.2				-0.5			
95% CI	-9.9, 7.4				-9.8, 8.8			
Non-US								
N	83		87		93		98	
Success, n (%)	72	(86.7)	84	(96.9)	76	(81.7)	91	(92.9)
Failure, n (%)	11	(13.3)	3	(3.4)	17	(18.3)	7	(7.1)
Treatment Difference, %*	-9.8				-11.1			
95% CI	-18.0, -1.6				-20.5, -1.8			

* Augmentin XR minus Augmentin 875/125mg

Atypical Pathogens

The clinical success rates at test of cure were also assessed in the individual CAP studies based on whether patients had typical pathogens and/or seropositivity for atypical pathogens. Interestingly, for patients enrolled in the controlled CAP studies, the clinical response rates were not influenced by the presence of atypical pathogens.

Pooled Analyses

Additional supportive evidence for the efficacy of Augmentin XR is provided by the sponsor in an analysis in which the primary efficacy variable data were combined from the two principal controlled CAP studies.

MO COMMENT: *The protocols were similar enough in design to allow for such a pooled analysis. However, this pooled analysis is not identified as being prospectively planned.*

The clinical success rate at test of cure for the pooled Augmentin XR group was at least as good as the clinical success rate at test of cure for the combined Augmentin comparator group. The proportion of patients with clinical success for the PP population was 88.2% (284/322) for the combined Augmentin XR group compared with 91.8% (292/318) for the combined Augmentin group (treatment difference: -3.7%, 95% CI: -8.3, 1.0). Success rates in the ITT population supported the conclusion of non-inferior efficacy of Augmentin XR in the treatment of CAP (treatment difference: -4.6%, 95% CI: -9.8, 0.6).

In this pooled analysis, the effects of covariates (age and gender) were formally investigated by logistic regression modeling. The results demonstrated that in the analysis of treatment effects, there was no evidence of significant interactions between treatment and gender (P=0.65), or treatment and age (P=0.48).

Secondary Efficacy Variables

The results of the secondary efficacy variables described in this section are for clinical response at end of therapy and bacteriological response at end of therapy and test of cure. A complete assessment of all secondary efficacy variables is presented in Study 546 Clinical Report, Sections 5.3 and 5.4; Study 556 Clinical Report, Sections 5.3 and 5.4 .

Clinical Response at End of Therapy

In the two principal controlled CAP studies, rates of clinical success at end of therapy were high (>90%) in the Clinical PP population of both studies and consistent between treatment groups (Table 35). In Study 546 in the

Clinical PP population, 90.5% of the Augmentin XR group and 94.5% of the Augmentin 875/125mg group were clinical successes at end of therapy. In Study 556, the clinical success rate at end of therapy in the Clinical PP population was 93.0% in the Augmentin XR group and 93.3% in the Augmentin 1000/125mg group. The corresponding clinical success rates for the ITT population, were 85.5% and 89.2% for the Augmentin XR and Augmentin 875/125mg groups in Study 546, and 87.0% in the Augmentin XR group and 88.0% in the Augmentin 1000/125mg group in Study 556.

Although the studies were not designed to demonstrate non-inferiority for secondary endpoints, in both studies and for both populations, the lower limit of the 95% CI for the treatment difference (Augmentin XR – Augmentin comparator) was not less than the pre-specfied limit set for the primary efficacy variable (i.e., ≥-10% for Study 546 and ≥-15% for Study 556).

Bacteriological Response at Test of Cure and End of Therapy
The results of the analyses of bacteriological response at test of cure and end of therapy are provided below. As stated in the previous section, the studies were not designed to demonstrate non-inferiority for secondary efficacy variables and the small number of patients in the bacteriological response analyses do not allow conclusions to be drawn from the results.

At test of cure in Study 546, the bacteriological success rates 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. 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.

At end of therapy in Study 546, the bacteriological success rates for the Bacteriology PP population were 84.8% in the Augmentin XR group and 92.3% in the Augmentin 875/125mg group, with corresponding rates of 76.9% and 90.0% in the ITT population. In contrast, in Study 556, the rates of bacteriological success at end of therapy were slightly higher for Augmentin XR compared with the comparator Augmentin regimen: 90.9% and 85.3% for the Augmentin XR and Augmentin 1000/125mg groups in the Bacteriology PP population, with corresponding rates of 88.6% and 80.9% in the Bacteriology ITT population.

Bacteremia at screening:
Only a very small proportion of patients in Studies 546 and 556 (7/322, 2.2% in the Augmentin XR group and 7/318, 2.2%, in the combined comparator group, Clinical PP population) had a positive blood culture at screening. The number of bacteremic patients with *S. pneumoniae* was 4/7 in the combined Augmentin XR group and 6/7 in the comparator group. With the exception of one bacteremic patient with *S. pneumoniae* in Study 546 (on-therapy blood culture yielded no growth but patient was a clinical failure at end of therapy with presumed persistence), the remaining Augmentin XR-treated patients with bacteremia at screening were clinical successes at test of cure.

Principal Uncontrolled Study in CAP: Study 547

Study Design and Methodology

Study 547 was an uncontrolled study designed to assess the clinical and bacteriological efficacy and safety of Augmentin XR for 7 days in the treatment of patients with CAP. Although this principal study was still ongoing at the time of clinical cut-off for this submission, data from a prospectively defined interim analysis (based on June 19, 2000, cut-off for completion of study visits) are included in this summary. The study was designed to enroll approximately 1200 patients, with the interim analysis being conducted after one third of the patients had been enrolled. The total sample size of 1200 patients was based on obtaining at least 10 patients with evaluable penicillin-resistant isolates of *S. pneumoniae.*

The study was conducted globally in geographically diverse regions of the world. A non-comparative study design was chosen since no single comparative agent was available in all participating countries and also to maximize the number of bacteriologically evaluable patients treated with Augmentin XR.

Male or female patients aged at least 16 years of age, with a clinical and radiological diagnosis of CAP and who were able to tolerate oral therapy were entered into the study. The criteria for a diagnosis of CAP were similar to those used in the principal controlled Study 546. In addition, in Study 547, patients had to have a clinical presentation which suggested pneumococcal involvement based on at least two of the following: (i) sudden onset; (ii) chills; (iii) pleuritic chest pain; (iv) localized alveolar consolidation on chest radiograph; (v) Gram positive cocci on direct examination of Gram-stained smear of respiratory sample. Patients who were failures on previous antibacterial therapy (with the exception of those treated with prior Augmentin) provided they had gram-positive cocci on direct examination of a respiratory sample smear, were also included in the study.

As in the principal studies, patients could be treated as out-patients or hospitalized depending on clinical need. Patients were assessed on four occasions: at screening (Day 0), on-therapy (Day 3-5), end of therapy (Day 9-11) and test of cure (Day 28-35). As with study 546, the visit windows for the screening (Day –2 to 1), end of therapy (Day 8-15), and test of cure (Day 16-37) visits were extended.

Assessment of Efficacy and Statistical Methodology

In Study 547, the primary efficacy variable was the per patient bacteriological response at test of cure (extended window of Day 16-37) which was determined from the bacteriological outcome results for pathogens isolated from sputum, respiratory samples from invasive procedures, or blood by culture. As in the controlled CAP studies, only typical pathogens were considered in these evaluations.

Secondary efficacy variables included bacteriological response at end of therapy and clinical response at test of cure and end of therapy.

The populations defined for analysis were the same as for the controlled studies. In this study the Bacteriology ITT population was the primary population for analysis. Point estimates and 95% CIs were calculated for the primary and secondary efficacy parameters. The 95% CIs were calculated using the normal approximation to the binomial distribution, incorporating a continuity correction of one half.

Disposition and Characteristics of the Study Population

A total of 421 patients were included in the planned interim analysis of Study 547, which was comprised of patients who had completed all study visits on or before June 19, 2000, and whose data had been received by SmithKline Beecham. Of these 421 patients, 420 patients received study medication and were included in the ITT population. One patient was enrolled into the study but did not receive study medication and was treated with intravenous Augmentin instead. The disposition of patients in Study 547 is summarized in the following table.

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

	Augmentin XR

Population	2000/125mg b.i.d. 7 days
Enrolled	421
Received Study Medication (ITT)	420
Completed Study	369
Total Withdrawn	51
Clinical PP at End of Therapy	360
Clinical PP at Test of Cure	333
Bacteriology ITT	142
Bacteriology PP at End of Therapy	127
Bacteriology PP at Test of Cure	119

In the ITT population, 369/420 patients (87.9%) completed the study. Fifty one patients (12.1%) withdrew from the study. The most frequently reported reason for withdrawal was adverse experiences (19/420, 4.5%).

The Bacteriology ITT population comprised the 142 patients in the ITT population who had at least one typical pathogen identified at screening.

Protocol Violations

Of the 142 patients in the Bacteriology ITT population, a total of 15 patients (10.6%) were excluded at end of therapy and 23 patients (16.2%) were excluded at test of cure. The most frequent reason for exclusion at end of therapy was lack of medication compliance (5 patients, 3.5%) and the most frequent reason at test of cure was lack of visit compliance (6 patients, 4.2%).

Of the 420 patients in the ITT population, a total of 60 patients (14.3%) were excluded from the Clinical PP at end of therapy and 87 patients (20.7%) were excluded from the Clinical PP at test of cure. The most frequent reason for exclusion at end of therapy was lack of medication compliance (25 patients, 6.0%) and at test of cure the most frequent reason for exclusion was lack of visit compliance (36 patients, 8.6%).

Demographic Characteristics

The demographic characteristics of patients in Study 547 are summarized in the following table (ITT and Bacteriology ITT populations).

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

	Augmentin XR 2000/125mg b.i.d. 7 days	
Demographic Characteristic	**ITT N=420**	**Bacteriology ITT N=142**
Gender, n (%)		
Male	236 (56.2)	94 (66.2)
Female	184 (43.8)	48 (33.8)
Race, n (%)		
White	274 (65.2)	107 (75.4)
Black	30 (7.1)	11 (7.7)
Oriental	68 (16.2)	14 (9.9)
Other*	48 (11.4)	10 (7.0)
Age (yrs)		
Mean (SD)	49.4 (18.8)	45.8 (18.6)
Range	16-93	16-88

* Other, as recorded by the investigator, were: ITT population, Hispanic (30 patients), mixed race (17 patients) and Indian (1 patient); Bacteriology ITT population, Hispanic (5 patients) and mixed race (5 patients).

There was a higher proportion of males than females in both the Bacteriology ITT (66.2%) and ITT (56.2%) populations. The mean age of patients was 45.8 years in the Bacteriology ITT population and slightly older in the ITT population, 49.4 years. The predominant racial origin of patients in both populations was white.

The proportion of patients in the Bacteriology ITT population hospitalized for treatment was 42.3% and 35.5% in the ITT population.

Bacteriology At Screening

Of the 142 patients that comprised the Bacteriology ITT population, 91 patients had only a typical pathogen identified from sputum, respiratory or blood sample pre-therapy and 51 patients had a typical pathogen isolated and were also seropositive for an atypical pathogen. Of those patients who had a typical pathogen at screening, 26.9% had an infection with a single pathogen.

There were an additional 89 patients who were seropositive for an atypical pathogen only, and therefore did not qualify for the Bacteriology ITT and PP populations. The key typical pathogens associated with CAP in this study are summarized in the following table.

Number (%) of Patients with Key Typical Pathogens Associated with CAP at Screening from All Sources: CAP Uncontrolled Study 547 (Bacteriology ITT and Bacteriology PP Test of Cure Population)

	Augmentin XR 2000/125mg b.i.d.			
Pre-Therapy Pathogen-n (%)	**Bacteriology ITT N=142**		**Bacteriology PP N=119**	
Total *S. pneumoniae*	58	(40.8)	52	(43.7)
Single pathogen *S. pneumoniae*	24	(16.9)	22	(18.5)
Total *H. influenzae*	48	(33.8)	39	(32.8)
Single pathogen *H. influenzae*	23	(16.2)	19	(16.0)
Total *H. parainfluenzae*	20	(14.1)	14	(11.8)
Single pathogen *H. parainfluenzae*	9	(6.3)	7	(5.9)
Total MSSA*	12	(8.5)	12	(10.1)
Single pathogen MSSA	7	(4.9)	7	(5.9)
Total *K. pneumoniae*	9	(6.3)	7	(5.9)
Single pathogen *K. pneumoniae*	2	(1.4)	1	(0.8)
Total *M. catarrhalis*	6	(4.2)	5	(4.2)
Single pathogen *M. catarrhalis*	2	(1.4)	2	(1.7)

* Only patients with methicillin-susceptible *S. aureus* (MSSA) isolates are included in this table. Three patients (included in both the ITT and Bacteriology PP populations) had methicillin-resistant *S. aureus* isolates. (MRSA)

The most prevalent typical pathogen identified in sputum, respiratory samples or blood in the Bacteriology ITT population at screening was *S. pneumoniae*. Approximately 40% of patients in the Bacteriology ITT population from whom *S. pneumoniae* was isolated presented with single pathogen infections.

Twelve patients were bacteremic at screening in the Bacteriology ITT population. Eleven patients (2.6%) had one typical pathogen identified from blood culture, and one patient had two blood pathogens isolated. *S. pneumoniae* was the most prevalent typical pathogen isolated from blood, identified in 6 patients. Ten of these twelve had bacteremia with organisms which are typical etiologies for pneumonia such as *S. pneumoniae, H. influenzae*, and *H. parainfluenzae*. Two patients with bactermia are described in greater detail in the efficacy section had bactermia with organisms which are considered unusual causes of CAP. The two patients had Bacteremia due to *Salmonella enteritidis* and *Proteus mirabilis* respectively.

Of the 51 patients in the Bacteriology ITT population who were also seropositive for an atypical pathogen, there were 38 seropositive results for *M. pneumoniae*, 15 seropositive results for *C. pneumoniae* and one seropositive result each for *C. psittaci* and *L. pneumophila*.

Of the key typical pathogens (*S. pneumoniae, H. influenzae, H. parainfluenzae,* and MSSA) that had an MIC performed, all but one were susceptible to amoxicillin/clavulanic acid, based on breakpoints defined by the NCCLS, 2000.

Two *S. pneumoniae* isolates were resistant to penicillin. These PRSP were also resistant to macrolides, oral cephalosporins and trimethoprim/sulfamethoxazole. Two further *S. pneumoniae* isolates were resistant to macrolides.

Overall, in the Bacteriology ITT population at screening, nine *H. influenzae* isolates (18.8%), one *H. parainfluenzae* isolate (5.0%) and ten MSSA isolates (83.3%) produced beta-lactamase.

Efficacy Results of Principal Uncontrolled CAP Study

The primary efficacy variable in this non-comparative study was the per patient bacteriological response at test of cure for the Bacteriology ITT population. The proportion of patients with a bacteriological response of success or failure at test of cure, together with 95% CIs for the Bacteriology ITT and Bacteriology PP populations, are shown in the following table.

Bacteriological Response at Test of Cure: CAP Uncontrolled
Study 547 (Bacteriology ITT and Bacteriology PP Populations)

	Augmentin XR 2000/125mg b.i.d. for 7 days	
Bacteriology ITT	**N=142**	
Success, n (%)	119	(83.8)
Failure, n (%)	23	(16.2)
Known Failure, n (%)	17	(12.0)
Unable to Determine, n (%)	6	(4.2)
95% CI for Success		76.5, 89.2
Bacteriology PP	**N=119**	
Success, n (%)	105	(88.2)
Failure, n (%)	14	(11.8)
95% CI for Success		80.7, 93.2

At test of cure the per patient bacteriological success rate was 83.8% for the Bacteriology ITT population and 88.2% for the Bacteriology PP population.

Although the number of patients in the Bacteriology populations of Studies 546 and 556 were small, the success rates in Study 547 are similar to the results for Augmentin XR for 10 days in controlled CAP Study 556 and the Augmentin comparator regimens in both controlled CAP studies. Augmentin XR for 7 days in CAP Study 546 had a lower bacteriological response rate at test of cure (Bacteriology ITT: 69.2%; Bacteriology PP: 78.1%).

The observed case analysis of bacteriological response at test of cure in Study 547 showed results similar to Study 556, with a bacteriological success rate in the Bacteriology ITT population of 87.5% (95% CI 80.5, 92.3) and demonstrated consistency with the conservative approach of the principal analysis.

Secondary Efficacy Variable

The results of the key secondary efficacy variables (i.e., bacteriological response at end of therapy and clinical response at test of cure and end of therapy) are described in this section. All secondary efficacy variables are presented in Study 547 Clinical Report.

Bacteriological Response at End of Therapy
At end of therapy, the bacteriological success rate was 88.0% for the Bacteriology ITT and 91.3% for the Bacteriology PP population.

The results of the analysis of bacteriological response at end of therapy are presented in the following table.

Bacteriological Response at End of Therapy: CAP Uncontrolled Study 547 (Bacteriology ITT and Bacteriology PP Populations)

	Augmentin XR 2000/125mg b.i.d. for 7 days
Bacteriology ITT	**N=142**
Success, n (%)	125 (88.0)
Failure, n (%)	17 (12.0)
Known Failure, n (%)	14 (9.9)
Unable to Determine, n (%)	3 (2.1)
95% CI for Success	81.3, 92.7
Bacteriology PP	**N=127**
Success, n (%)	116 (91.3)
Failure, n (%)	11 (8.7)
95% CI for Success	84.7, 95.4

Clinical Response at Test of Cure and End of Therapy
Clinical success rates at test of cure and end of therapy were similar to the rates reported for the controlled CAP studies.

The results of the analysis of clinical response at test of cure and end of therapy are presented in the following table.

Clinical Response at Test of Cure and End of Therapy: CAP Uncontrolled Study 547 (Clinical PP and ITT Populations)

	Augmentin XR 2000/125mg b.i.d. for 7 days	
ITT	**Test of Cure N=420**	**End of Therapy N=420**
Success, n (%)	347 (82.6)	364 (86.7)
Failure, n (%)	73 (17.4)	56 (13.3)
Clinical Failure, n (%)	36 (8.6)	36 (8.6)
Clinical Recurrence, n (%)	8 (1.9)	- -
Unable to Determine, n (%)	29 (6.9)	20 (4.8)
95% CI for Success	78.6, 86.1	83.0, 89.7
Clinical PP*	**N=333**	**N=360**
Success, n (%)	297 (89.2)	331 (91.9)
Failure, n (%)	36 (10.8)	29 (8.1)
95% CI for Success	85.2, 92.2	88.5, 94.4

Data Source: Study 547, Section 11, Table 11.43c, Table 11.43d, Table 11.30c, Table 11.30d; Study 547, SAS Datasets.
* Data are for the Clinical PP population included in either the test of cure or end of therapy analyses.

Bacteriological and Clinical Response in Bacteremic Patients
At test of cure in the Bacteriology ITT population, 9 out of the 12 bacteremic patients (75.0%) had a clinical and bacteriological response of success. In the Bacteriology PP population at test of cure, 7 of 8 bacteremic patients (87.5%) had both a clinical and bacteriological response of success and one patient had a clinical response of failure with bacteriological presumed persistence carried forward from the end of therapy visit.

All six patients in the Bacteriology ITT population with positive blood cultures for *S. pneumoniae* (all penicillin-susceptible) were clinical and bacteriological successes at test of cure. Repeat blood culture was negative in all cases. It should be noted that in accordance with the protocol definition, bacteriological outcome was presumed eradicated due to the absence of an evaluable sputum at end of therapy.

There were three patients in the ITT population with bacteremia who failed therapy. Patient 547.086.06439 who at screening had blood cultures positive for H. parainfluenzae (susceptible) and Prevotella species. This patient was a clinical failure and therefore, became a microbiological failure. Patient 547.173.06898 had *Proteus mirabilis* (susceptible) isolated from the blood at screening and was a clinical success at end of therapy. However, she was lost to follow up and, therefore, was categorized as both a clinical and microbiological failure. The final failure was a patient who had Salmonella enteritidis bacteremia and a beta-lactamase negative *H. influenzae* isolated from sputum on screening. This patient developed a necrotizing pneumonia with throacic empyema and typhoid fever and was considered to be a clinical failure at end of therapy. This patient did not produce sputum at end of therapy and therefore was considered to have presumed bacteriological persistence.

Results of Eradication of Key Typical Pathogens in Combined CAP Studies 546, 547 and 556

The overall eradication of key pathogens associated with CAP (combined pathogen outcomes of eradication and presumed eradication), was assessed by pooling data from the Augmentin XR groups of the three principal studies (Studies 546, 547 and 556) at test of cure and end of therapy. If a patient had more than one type of pathogen, this patient is included in the count for each individual micro-organism. However, if the patient had more than one isolate of the same pathogen, they are counted only once for each pathogen.

In the majority of patients who were not bacteremic at screening, it was not possible to bacteriologically confirm the eradication of screening pathogens since repeat sputum or respiratory samples could not be provided due to clinical improvement. As a result, only a small number of pathogens were documented as eradicated: 3.2% (7/216) of pathogens from Augmentin XR patients and 4.3% (3/69) of pathogens from Augmentin comparator patients in the Bacteriology PP population at test of cure.

In the following table, the overall eradication of pathogens for the pooled Augmentin XR group are compared with the overall eradication of pathogens for the pooled comparator group (i.e., Augmentin 875/125mg b.i.d. and Augmentin 1000/125mg tid, from Studies 546 and 556 respectively). Pathogens confirmed eradicated and pathogens presumed eradicated (based on clinical success) are combined.

Number (%) of Patients with Bacteriological Outcome of Eradicated or Presumed Eradicated by Pre-Therapy Pathogen: Combined CAP Studies 546, 547 and 556 (Bacteriology PP and Bacteriology ITT Populations)

	Combined CAP 7 and 10 Day Studies 546, 547 and 556

	Bacteriology PP**				Bacteriology ITT			
Test of Cure	**Augmentin XR N=183**		**Augmentin Comparators N=58**		**Augmentin XR N=225**		**Augmentin Comparators N=77**	
	*n/N**	%	*n/N**	%	*n/N**	%	*n/N**	%
All Pathogens	189/216	(87.5)	56/69	(81.2)	219/273	(80.2)	72/92	(78.3)
S. pneumoniae	72/78	(92.3)	21/24	(87.5)	81/91	(89.0)	23/28	(82.1)
H. influenzae	44/50	(88.0)	13/17	(76.5)	52/65	(80.0)	16/23	(69.6)
H. parainfluenzae	18/21	(85.7)	8/9	(88.9)	22/27	(81.5)	10/11	(90.9)
MSSA	14/18	(77.8)	1/2	(50.0)	14/19	(73.7)	3/5	(60.0)
M. catarrhalis	9/10	(90.0)	1/2	(50.0)	11/13	(84.6)	3/4	(75.0)
K. pneumoniae	8/10	(80.0)	2/2	(100.0)	10/13	(76.9)	2/2	(100.0)
End of Therapy	**N=193**		**N=60**		**N=225**		**N=77**	
	*n/N**	%	*n/N**	%	*n/N**	%	*n/N**	%
All Pathogens	210/230	(91.3)	61/72	(84.7)	236/273	(86.4)	76/92	(82.6)
S. pneumoniae	76/81	(93.8)	21/24	(87.5)	85/91	(93.4)	23/28	(82.1)
H. influenzae	50/54	(92.6)	14/17	(82.4)	58/65	(89.2)	18/23	(78.3)
H. parainfluenzae	21/24	(87.5)	9/9	(100.0)	22/27	(81.5)	11/11	(100.0)
MSSA	16/19	(84.2)	2/3	(66.7)	16/19	(84.2)	3/5	(60.0)
M. catarrhalis	10/10	(100.0)	1/2	(50.0)	12/13	(92.3)	3/4	(75.0)
K. pneumoniae	10/11	(90.9)	2/2	(100.0)	11/13	(84.6)	2/2	(100.0)

* *n/N*= number of patients with pathogen eradicated or presumed eradicated / number of patients with pathogen.
** Data are for the Bacteriology PP population included in either the test of cure or end of therapy analyses.
Notes: 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.
Augmentin Comparators=Augmentin 875/125 mg b.i.d. (Study 546) and Augmentin 1000/125 mg tid (Study 556)

At test of cure, the overall pathogen eradication rates were similar between the pooled Augmentin XR group and the pooled Augmentin comparator group for both the Bacteriology PP and Bacteriology ITT populations (Bacteriology PP: Augmentin XR 87.5% versus Augmentin comparators 81.2%; Bacteriology ITT: Augmentin XR 80.2% versus Augmentin comparators 78.3%).

S. pneumoniae and *H. influenzae*, the most frequently isolated pathogens in this combined study population of CAP patients, had eradication rates at test of cure in the Augmentin XR group of 92.3% and 88.0%, respectively (Bacteriology PP population). For the pooled comparator Augmentin group in the Bacteriology PP population, the corresponding rates for these pathogens were 87.5% and 76.5%. Eradication rates at test of cure for these pathogens in the Bacteriology ITT population were slightly lower in both treatment groups.

At end of therapy in the Bacteriology PP population, 91.3% of initial pathogens in the pooled Augmentin XR group were either eradicated or presumed eradicated compared with 84.7% in the comparator Augmentin group. The eradications rates for each of the key pathogens shown in the previous table were consistently high in both treatment groups. The results for the Bacteriology ITT population were similar to the Bacteriology PP population at this assessment.

Resistant Pathogens
In the Bacteriology PP test of cure population, four patients in the pooled Augmentin XR group (all in the 7 day treatment duration) and two patients in the pooled Augmentin comparator group (one in each comparator regimen) had PRSP. All of the PRSP isolates demonstrated resistance to two or more classes of antibacterial agents. Three patients with PRSP (two of which were macrolide-resistant) in the Augmentin XR group were clinical and bacteriological successes at test of cure (*S. pneumoniae* presumed eradicated). One Augmentin XR-treated patient with PRSP (penicillin MIC of 4μg/mL and erythromycin MIC of 4μg/mL) and *K. pneumoniae* was a clinical and bacteriological success at end of therapy but a clinical and bacteriological failure at test of cure (bacteriological outcome of presumed failure). In the comparator group, one patient

(Augmentin 875/125mg) was a clinical and bacteriological success at test of cure, with *S. pneumoniae* presumed eradicated, and one patient (Augmentin XR 1000/125mg) was a clinical and bacteriological failure, with PRSP isolated at end of therapy. This patient received study treatment for 3 days, then was withdrawn for insufficient therapeutic effect.

Of the seven Augmentin XR patients with macrolide-resistant *S. pneumoniae*, five were clinical and bacteriological successes at test of cure and two (one described above with PRSP) were clinical and bacteriological failures; in both cases, the bacteriological outcome was presumed persistence.

The majority of beta-lactamase producing strains of *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis* and MSSA were eradicated or presumed eradicated. The number of beta-lactamase producers and non-producers were too small to make meaningful comparisons by genus and species.

A brief overview of the bacteriological outcome for PRSP (penicillin MIC≥2μg/mL), macrolide-resistant *S. pneumoniae* (erythromycin MIC ≥1μg/mL) and key beta-lactamase producing strains for the pooled Augmentin XR group from Studies 546, 547 and 556, and the pooled comparator Augmentin group from Studies 546 and 556 (ie Augmentin 875/125mg b.i.d. and Augmentin 1000/125 mg tid) is provided in the table below.

Number (%) of Patients 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 and 556 (Bacteriology PP and Bacteriology ITT Populations)

	Combined CAP 7 and 10 Day Studies 546, 547 and 556			
	Augmentin XR		Augmentin Comparators	
Bacteriology PP	N=183 *n/N**	%	N=58 *n/N**	%
Penicillin-resistant *S. pneumoniae* (≥2μg/mL)	3/4	(75.0)	1/2	(50.0)
Erythromycin Resistant *S. pneumoniae* (≥1μg/mL)	5/7	(71.4)	2/3	(66.7)
Beta-Lactamase Positive *H. influenzae*	10/10	(100.0)	1/1	(100.0)
Beta-Lactamase Positive *H. parainfluenzae*	1/1	(100.0)	1/1	(100.0)
Beta-Lactamase Positive MSSA	11/15	(73.3)	1/2	(50.0)
Beta-Lactamase Positive *M. catarrhalis*	9/10	(90.0)	1/2	(50.0)
Bacteriology ITT	N=225			N=77
Penicillin-resistant *S. pneumoniae* (≥2μg/mL)	4/5	(80.0)	1/3	(33.3)
Erythromycin Resistant *S. pneumoniae* (≥1μg/mL)	7/9	(77.8)	2/4	(50.0)
Beta-Lactamase Positive *H. influenzae*	11/12	(91.7)	2/3	(66.7)
Beta-Lactamase Positive *H. parainfluenzae*	2/2	(100.0)	2/2	(100.0)
Beta-Lactamase Positive MSSA	11/16	(68.8)	2/4	(50.0)
Beta-Lactamase Positive *M. catarrhalis*	10/12	(83.3)	3/4	(75.0)

* *n/N* = number of isolates which were eradicated or presumed eradicated / number of isolates with MIC or beta-lactamase data for the pathogen.
Notes: If a patient had more than one isolate of a specified pathogen with MIC or beta-lactamase data, all of the isolates have been included. Augmentin Comparators=Augmentin 875/125 mg b.i.d. (Study 546) and Augmentin 1000/125 mg tid (Study 556)

New Pathogens

In the Bacteriology PP and Bacteriology ITT populations for the pooled Augmentin XR group from the three principal CAP studies at test of cure, one patient had colonization with *M. catarrhalis*. In the pooled

Augmentin comparator group at test of cure, one patient had a new infection with *M. catarrhalis* (Bacteriology PP and Bacteriology ITT populations) and two patients had colonization with *H. parainfluenzae* and *Serratia liquefaciens*, respectively.

In the pooled Augmentin XR group, a total of six patients in the Bacteriology PP population had new pathogens identified at end of therapy (two superinfections and four colonizations). In the Bacteriology ITT population at this assessment, the corresponding number was 8 patients (three patients with superinfections, three patients with colonization by one pathogen, and two patients with colonization by > 1 pathogen). For the pooled Augmentin comparator group at end of therapy, in both Bacteriology PP and Bacteriology ITT populations there were one patient with superinfection and nine patients with colonization.

Only a small number of patients had persistent or recurrent pathogens recovered at end of therapy or test of cure.

Assessment of Treatment Failures in CAP Studies

The clinical and microbiology data available for the Bacteriology PP populations allow an evaluation of treatment failures to be made. Data for treatment failures in the Bacteriology PP populations of the three studies were reviewed taking into account any pathogen MIC data and relevant clinical features. No consistent predictive factor could be identified. Only a relatively small number of patients had pathogens that persisted at end of therapy or recurred at test of cure. In the few cases where there was documented persistence or recurrence of the initial pathogen, the MICs for amoxicillin/ clavulanic acid were low and had not increased between screening and the time of failure. The MIC's were within the expected range of variation (plus or minus one doubling dilution).

Augmentin XR patients who were treatment failures and had *S. pneumoniae* isolated at screening are briefly reviewed below by study.

Study 546: Seven patients in the Augmentin XR group had a clinical and/or bacteriological response of failure at test of cure in the Bacteriology PP population. Six patients had a clinical response of failure and were all presumed bacteriological failures. One patient was a clinical success and a known bacteriological failure (546.104.00368). This patient was not treated with additional antibiotics and clinical assessment at test of cure visit was consistent with a successful clinical outcome.

Two patients in the Augmentin XR group with a clinical and/or bacteriological response of failure at test of cure had *S. pneumoniae* isolated at screening. Patient 546.400.00858 with a monomicrobial infection of penicillin susceptible *S. pneumoniae* was also bacteremic at screening. An on-therapy blood culture yielded no growth. At end of therapy, the clinical and bacteriological response was failure, with a bacteriological outcome of presumed persistence (due to no evaluable sputum). Rales, mild dyspnea and mild pleuritic pain persisted although an improvement in sputum characteristics was noted and radiological findings were improved. Patient 546.022.00326 had a polymicrobial infection of a penicillin susceptible *S. pneumoniae* and beta-lactamase positive MSSA and was a clinical failure at end of therapy with a bacteriological outcome of presumed persistence.

Study 547: Fourteen patients treated with Augmentin XR had a clinical and/or bacteriological response of failure at test of cure in the Bacteriology PP population. Of the thirteen patients with clinical failure, two patients were known bacteriological failures (547.083.06673; 547.086.06444) and 11 patients were presumed bacteriological failures. One patient was a clinical success and a known bacteriological failure (547.331.06874). This patient was not treated with additional antibiotics and clinical assessment at test of cure visit was consistent with a successful clinical outcome.

Four patients in the Augmentin XR group with a clinical and/or bacteriological response of failure at test of cure had *S. pneumoniae* isolated at screening. Three patients (547.084.06400, 547.210.08354 and 547.213.08692) had a monomicrobial infection with penicillin-susceptible *S. pneumoniae* at screening and were both clinical failures and bacteriological failures at end of therapy with presumed bacteriological

persistence (Patients 547.084.06400 and 547.213.08692 were also seropositive for *C. psittaci* and *M. pneumoniae,* respectively). The fourth patient with *S. pneumoniae*, Patient 547.376.14972, had a PRSP (penicillin MIC 4µg/mL, and amoxicillin/clavulanic acid MIC 8µg/mL) and a *K. pneumoniae* (amoxicillin/clavulanic acid MIC 2µg/mL) isolated from sputum at screening. At end of therapy, this patient was a clinical and bacteriological success (presumed eradication of both pathogens) but at test of cure, the clinical and bacteriological responses were failure and the bacteriological outcome was presumed failure for both pathogens) This patient was seropositive for *M. pneumoniae.*

Study 556: Three patients in the Augmentin XR group had a clinical and/or bacteriological response of failure at test of cure in the Bacteriology PP population. Of two patients with a clinical response of failure, one was a known bacteriological failure due to a superinfection (556.304.02457) and one was a presumed bacteriological failure (556.066.02689). One patient was a clinical success and a known bacteriological failure (556.605.02806). This patient was not treated with additional antibiotics and clinical assessment at test of cure visit was consistent with a successful clinical outcome. None of these patients had *S. pneumoniae* at screening.

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

	Success Rate		
	Augmentin XR % (n/N)	**Augmentin* % (n/N)**	**Treatment Difference % (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)
Combined 546/556	88.2% (284/322)	91.8% (292/318)	-3.7 (-8.3, 1.0)
Study 547	89.2% (297/333)	-	(85.2, 92.2)
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)
Combined 546/556	79.2% (336/424)	83.9% (364/434)	-4.6 (-9.8, 0.6)
Study 547	82.6% (347/420)	-	(78.6, 86.1)
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 547	88.2% (105/119)	-	(80.7, 93.2)
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 547	83.8% (119/142)	-	(76.5, 89.2)

* Comparators were Augmentin 875/125mg b.i.d. for 7 days (Study 546) and Augmentin 1000/125mg tid for 10 days (Study 556).

** Non-inferiority limit was prospectively defined as ≥-10% for Study 546, ≥-15% for Study 556 and ≥-10% for the combined analysis of the two studies. Treatment difference not applicable for non-comparative Study 547.

Note Due to insufficient numbers in the Bacteriology PP and Bacteriology ITT populations it was not appropriate to perform the analysis for heterogeneity, and hence the pooled analysis of bacteriological response was not conducted.

Conclusions

The principal conclusions of the efficacy assessment of Augmentin XR in CAP are as follows:

• In two principal controlled clinical studies, Studies 546 and 556, adequate clinical success rates at test of cure (primary efficacy variable) were achieved with Augmentin XR 2000/125mg twice daily for 7 and 10 days respectively, that were comparable with published data for Augmentin in the treatment of CAP:

- In Study 556, the efficacy of Augmentin XR 2000/125mg twice daily for 10 days was concluded to be at least as good as that of Augmentin 1000/125mg tid for 10 days, in terms of the clinical response at test of cure.

- In Study 546, the lower bound of the 95% CI for the treatment difference in the clinical success rate at test of cure fell just outside the -10% limit to conclude non-inferiority of Augmentin XR compared with Augmentin 875/125mg b.i.d. for 7 days. This failure can be explained by the non-U.S. (particularly German) centers where the active control group had an efficacy rate which was very high. Analysis of efficacy by country group indicated that in US patients the non-inferiority criterion of –10% was achieved; in non-US patients a statistically significant difference in favor of Augmentin 875/125mg b.i.d. was observed.

• Augmentin XR was shown to be as effective as comparators, with proven efficacy in the treatment of CAP, in the pooled analysis of both principal studies.

• No significant interaction between treatment and age was identified in the covariate analysis.

• In one principal uncontrolled study, Study 547, a high per patient bacteriological success rate (primary efficacy variable) and clinical success rate were demonstrated with Augmentin XR 2000/125mg twice daily for 7 days at test of cure.

• In the three principal CAP studies, the results for the primary efficacy variable were consistent between the PP and ITT populations.

• Augmentin XR successfully eradicated key pathogens associated with CAP namely, *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, MSSA, *M. catarrhalis* and *K. pneumoniae*, including strains possessing resistance mechanisms.

Although these data support the indication of Augmentin XR (2000/125mg twice daily for 7 or 10 days) for the treatment of CAP, they do not support an indication of CAP due to PRSP because of a very limited number of patients who were found to have PRSP. Efficacy against PRSP in CAP was a primary program objective as communicated to the division, and this was not demonstrated based on data in this submission. Efficacy against PRSP would have constituted a significant benefit conferred by the increased amoxicillin content of Augmentin XR.

AUGMENTIN XR CLINICAL PROGRAM IN

The efficacy of Augmentin XR (2000/125mg b.i.d. for 7 days) is demonstrated in two principal well-controlled clinical studies (Studies 548 and 549).

Clinical Studies of Augmentin XR in —

Study	Treatment Regimen	Duration	N*	Geographic Region
Principal Controlled Studies				
548	Augmentin XR 2000/125mg b.i.d.	7 days	314	US and Mexico
	Clarithromycin 500mg b.i.d.	7 days	320	
549	Augmentin XR 2000/125mg b.i.d.	7 days	332	US and Europe
	Levofloxacin 500mg qd	7 days	341	

* N=number of patients randomized to treatment.

MO COMMENT: The design of both studies was consistent with current FDA draft guidance for the study of —

Principal Controlled Studies in — Studies 548 and 549

Study Design and Methodology
Studies 548 and 549 were both 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 established antibacterial regimens used in clinical practice for —

In Study 548, the macrolide clarithromycin was selected using the standard highest approved — dose regimen of 500mg twice daily for 7 days. In study 549, levofloxacin was selected as the active comparator using the approved dose regimen in the US of 500mg once daily for 7 days.

Patients participating in Studies 548 and 549 were representative of the population with well-defined — without serious complications, and suitable for treatment with an oral antibacterial agent. Male or female patients aged ≥40 years were selected who met clinical criteria for — , based on a definition that followed FDA guidelines for studies in this indication. In particular, patients were to have:

• A history of ——— characterized by cough and sputum production for at least two consecutive years and for most days in a consecutive three-month period in each year.

• A current episode of — characterized by increased purulent sputum together with increased cough and increased dyspnea.

A list of exclusion criteria prevented patients from entering the study who had a clinical diagnosis of pneumonia, cystic fibrosis, active tuberculosis, active bronchiectasis, or active pulmonary malignancies or any patients who had a complicating infection or disease that would compromise evaluation of the study medication. Patients who required parenteral antibacterial therapy, patients who had received any other systemic antibacterial agent within 7 days of study entry, or patients who were receiving systemic corticosteroids at a dose of >10 mg per day of prednisone (or equivalent), were also excluded. Other standard exclusion criteria related to renal impairment, impaired liver function, other serious underlying diseases or drug reactions, and in female patients, pregnancy, lactation or inadequate birth control method.

Patients eligible to receive study medication were randomly assigned to receive either Augmentin XR or the active comparator in a double-blind fashion. Treatment could be administered either to out-patients or to hospitalized patients, depending on clinical need. After screening, patients were expected to attend the clinic for an on-therapy visit (Day 3-5), an end of therapy visit (Day 9-11), a test of cure visit (Day 14-21) and a long-term follow-up visit (Day 28-35). For the purposes of analysis before the blind was broken, visit

windows for screening, end of therapy and test of cure were extended to Day –2 to 1, Day 8 to 13 and Day 14 to 23 respectively.

At the clinic visits, the signs and symptoms associated with [redacted] (cough, dyspnea, sputum characteristics) and auscultatory findings (presence or absence of wheeze, rales and crackles), were assessed to determine clinical outcome. Sputum samples were collected, if possible, for microscopic evaluation of purulence and bacteriology. Bacteriology included Gram staining, routine culture of aerobic bacteria and identification of isolates to the genus and species level. Susceptibility testing of all aerobic pathogens to a range of antibacterial agents was conducted according to NCCLS guidelines. *Haemophilus* spp., *M. catarrhalis*, *Enterococcus* spp. and *S. aureus* were also tested for beta-lactamase production.

Assessment of Efficacy and Statistical Methodology

Efficacy Variables
The primary efficacy variable in the two principal controlled studies was the clinical response (success or failure) at test of cure (extended window of Day 14-23 assessment). The choice of primary endpoint is in accordance with the draft regulatory guidance for this indication and is the endpoint of most importance to the patient.

For patients who were clinical successes at end of therapy, clinical response at test of cure was based on the changes in signs and symptoms of [redacted] i.e., severity of cough and dyspnea, auscultatory findings and evaluation of sputum characteristics) from the screening assessment. The investigator first assigned a clinical outcome of either clinical success, clinical recurrence or unable to determine. Clinical response at test of cure was then determined as follows:

Determination of Clinical Response at Test of Cure

Clinical Outcome	**Clinical Response**
- Test of cure clinical success	⇒ ***Clinical Success***
- Clinical recurrence at test of cure	⇒ ***Clinical Failure***
- Unable to determine at test of cure	
- Clinical failure at end of therapy	⇒ ***Clinical Failure***
- Unable to determine at end of therapy	

It is important to note that clinical outcome was evaluated at test of cure only if the patient was a clinical success at end of therapy. Patients with a clinical outcome of failure or unable to determine at end of therapy were automatically counted as a failure at subsequent time points.

Secondary efficacy variables presented in this ISE include clinical response at end of therapy and bacteriological response at end of therapy and test of cure.

Each patient's bacteriological response at test of cure and end of therapy was determined from the bacteriological outcome results for pathogens isolated from sputum. For patients with a pre-therapy pathogen but without an evaluable sample at the end of therapy or test of cure due to clinical improvement, bacteriological outcome was presumed eradicated on the basis of clinical outcome. Similarly a bacteriological outcome of presumed failure at test of cure or presumed persistence at end of therapy was assigned in the case of clinical failures with no evaluable sputum sample. The patient's bacteriological response combined information on initial and new pathogens. Bacteriological success was defined as the eradication, or presumed eradication of all pre-therapy pathogens without superinfection or new infection, but with or without colonization. Bacteriological outcomes of failure or presumed failure, or unable to determine, for one or more initial pathogens were automatically counted as a failure at subsequent timepoints.

Data Sets for Analysis
Four patient populations were defined for the analysis of clinical and bacteriological efficacy as follows:

- **Intent-to-treat (ITT):** all randomized patients who took at least one dose of study medication.

- **Clinical Per Protocol (PP):** a subset of the ITT population that excluded patients who violated the protocol to an extent that could affect treatment efficacy.

- **Bacteriology ITT:** all randomized patients who took at least one dose of study medication and had at least one typical pre-therapy pathogen identified at screening.

- **Bacteriology PP**: a subset of the Bacteriology ITT population (i.e., all patients had at least one typical pre-therapy pathogen) which excluded patients who violated the protocol to an extent that could affect treatment efficacy.

Statistical Methodology

The two principal — studies were designed to demonstrate that Augmentin XR was at least as good as the active comparator. In both studies the planned sample size of 600 patients (to provide 444 clinically evaluable patients) was calculated based on an estimated clinical response rate of 88% at test of cure. The estimation of sample size used 90% power to show that the lower bound of the two-sided 95% CI for the difference in response rates (Augmentin XR minus comparator) was no less than the pre-defined non-inferiority limit of –10%. The selection of the –10% limit followed a more conservative approach than outlined in FDA guidance. The analysis of the primary and secondary response variables was based on an unstratified comparison of proportions between the treatment groups. Two-sided 95% CIs were used to estimate the difference in the proportion of successes between the treatment groups. All CIs for differences in proportions were calculated using the normal approximation to the binomial distribution. For the primary efficacy variable, the non-inferior efficacy of Augmentin XR was concluded if the lower limit of the CI was greater than or equal to the non-inferiority limit (i.e., -10%). The studies were not designed to demonstrate non-inferiority for secondary efficacy variables.

The efficacy of Augmentin XR in the treatment of — is supported primarily by the results from each of the individual studies. A pooled analysis of the two studies was conducted to provide additional evidence of the clinical and bacteriological response in the total population of — patients at test of cure. The pooled analysis was based on an overall estimate of the treatment difference in proportion of successes, stratified by study. The combined study population was also used to evaluate bacteriological outcome by pathogen at end of therapy and test of cure.

The pooled population dataset was also used to determine the clinical response at test of cure in subgroups of interest, specifically: age, gender, race, previous systemic corticosteroid use in the previous 12 months, percent predicted FEV1 at baseline, smoking pack-years and the number of exacerbations in previous 12 months treated with antibacterial agents. The effect of these covariates on the primary efficacy variable was investigated by logistic regression modeling, where a significance level of 5% was considered significant for main effects and 10% for treatment-covariate interactions.

Disposition and Characteristics of the Study Populations

In the two principal — studies, patients were randomized on a 1:1 basis to receive treatment with either Augmentin XR or comparator. In Study 548, a total of 634 patients were randomized to receive study medication (Augmentin XR: 314 patients, clarithromycin: 320 patients). The ITT population in Study 548 comprised 631 patients. After randomization, three patients (one Augmentin XR and two clarithromycin patients) withdrew consent and did not take any study medication. In Study 549, a total of 673 patients were randomized to receive study medication (Augmentin XR: 332 patients, levofloxacin: 341 patients). In this study, one patient in each group was withdrawn before taking the first dose of study medication and so the ITT population comprised 671 patients.

In both studies, patients were included in the Bacteriology ITT population provided that they had at least one respiratory pathogen identified at screening from an evaluable sputum sample (i.e., a sputum sample with >25 WBC and <10 epithelial cells per field at 100x magnification). In Study 548, 23.0% of the Augmentin XR group (72/313 patients) and 21.7% of the clarithromycin group (69/318 patients) met this criterion and

comprised the Bacteriology ITT population. In Study 549 bacteriology recovery rates were slightly higher with 29.0% of the Augmentin XR group (96/331 patients) and 28.2% of the levofloxacin group (96/340 patients) included in the Bacteriology ITT population.

Only a small proportion of patients in each of the principal studies withdrew: 72 patients (11.4%) withdrew from Study 548 and 75 patients (11.2%) withdrew from Study 549. The most frequent reason for withdrawal in both studies was adverse experience. Only a very small number of patients withdrew due to insufficient therapeutic effect. There were no statistically significant differences between treatment groups in either study with respect to the total numbers of patients withdrawn or the numbers withdrawn due to an adverse experience.

Patient Disposition: Principal Controlled Studies 548 and 549

	Study 548				Study 549			
	Augmentin XR 2000/125mg b.i.d.		Clarithromycin 500mg b.i.d.		Augmentin XR 2000/125mg b.i.d.		Levofloxacin 500mg qd	
	n		n		n		n	
Randomized	314		320		332		341	
Received Study Medication (ITT)	313		318		331		340	
Completed study	274		285		294		302	
Reasons for Withdrawal (ITT), n (%):								
Adverse Experience	15†	(4.8)	11	(3.5)	17	(5.1)	18	(5.3)
Insufficient Therapeutic Effect	1†	(0.3)	2	(0.6)	3	(0.9)	1	(0.3)
Protocol Deviation *	12	(3.8)	9	(2.8)	12	(3.6)	13	(3.8)
Lost to Follow-Up	9	(2.9)	10	(3.1)	4	(1.2)	4	(1.2)
Other Reason**	2	(0.6)	1	(0.3)	1	(0.3)	2	(0.6)
Total Withdrawn, n (%)	39	(12.5)	33	(10.4)	37	(11.2)	38	(11.2)
Clinical PP at End of Therapy	253		267		279		290	
Clinical PP at Test of Cure	241		260		275		283	
Bacteriology ITT	72		69		96		96	
Bacteriology PP at End of Therapy	61		58		83		82	
Bacteriology PP at Test of Cure	52		56		80		74	

* Including non-compliance

** Other reasons for withdrawal, as determined by the investigator, were:

- in Study 548, 'patient withdrew consent; refused to continue' and 'patient withdrew consent' (2 patients).
- in Study 549, 'patient refused visit', 'patient's pneumologist changed the patient's study treatment drugs' and 'patient withdrawn from study by the sponsor'.

† Patient (548.211.07567) in the Augmentin XR group is correctly presented here as having been withdrawn from the study due to an adverse experience, instead of being withdrawn due to insufficient therapeutic effect as recorded in Study 548, Section 10, Table 10.07 and Study 548 SAS Datasets.

Protocol Violations

A summary of the proportion of patients excluded from the Clinical PP and Bacteriology PP populations at end of therapy and test of cure is presented in the following table.

Number (%) of Patients Excluded From the Clinical and Bacteriology PP Populations – — Principal Controlled Studies 548 and 549

Populations		Study 548 AugmentinXR	Clarithromycin	Study 549 AugmentinXR	Levofloxacin
ITT Population Clinical PP	**Visit**	**N=313**	**N=318**	**N=331**	**N=340**
n (%) excluded	End of Therapy	60 (19.2)	51 (16.0)	52 (15.7)	50 (14.7)
	Test of Cure	72 (23.0)	58 (18.2)	56 (16.9)	57 (16.8)
Bacteriology ITT Bacteriology PP	**Visit**	**N=72**	**N=69**	**N=96**	**N=96**
n (%) excluded	End of Therapy	11 (15.3)	11 (15.9)	13 (13.5)	14 (14.6)
	Test of Cure	20 (27.8)	13 (18.8)	16 (16.7)	22 (22.9)

There were no marked differences between the treatment groups in either of the studies in the incidence or pattern of exclusions from the Clinical PP populations at end of therapy and test of cure. In Study 548, the major reasons for exclusion from the Clinical PP population at test of cure in both treatment groups were lack of visit compliance, lack of medication compliance and clinical outcome of Unable to Determine. In Study 549, the major reasons for exclusion from the Clinical PP population at test of cure in both treatment groups were lack of visit compliance, clinical outcome of Unable to Determine, lack of medication compliance and violation of exclusion criteria, for example, diagnosis of pneumonia.

For the Bacteriology PP population in both studies some differences between the treatment groups emerged in the incidence of exclusions at test of cure. In Study 548 at test of cure, there was a greater proportion of patients excluded from the Augmentin XR group (27.8% excluded) than in the clarithromycin group (18.8% excluded), but the difference could not be attributed to any specific reason. In study 549, more patients were excluded from the levofloxacin group than the Augmentin XR group at test of cure (22.9% vs 16.7%), primarily due to a higher incidence of patients in the levofloxacin group with a bacteriological outcome of Unable to Determine.

Demographic and Baseline Characteristics

In both studies, the two treatment groups were generally well matched with respect to demographic and baseline disease characteristics. There were also no major differences evident between the ITT population and the Clinical PP populations.

The demographic characteristics of the ITT populations differed slightly between the two studies. In Study 548, the mean age of patients by treatment group was approximately 56 years and there was a slightly higher proportion of females than males, a feature most evident in the Augmentin XR group. Study 549 recruited a slightly older population compared with Study 548 with a mean age of approximately 60 to 62 years across the treatment groups, and there were a clearly higher proportion of males than females in each of the treatment groups. In both studies, the majority of patients were white. Similar observations were made for the Clinical PP population.

Disease history was similar between the studies. Patients had on average suffered from [redacted] for between 12 to 14 years and the majority of patients (73.7% in Study 548 and 78.1% Study 549, ITT population) had experienced between 1 and 4 exacerbations in the previous year that were treated with antibacterials. A small proportion of patients had experienced more than four exacerbations of [redacted] in the last year that required treatment with antibacterials (7.8% in Study 548 and 10.9% in Study 549, ITT population).

The demographic and baseline disease characteristics of the ITT populations in Studies 548 and 549 are shown in the following table.

Demographic and Baseline Characteristics: Principal Controlled Studies 548 and 549 (ITT Population)

Demographic/baseline Characteristic	Study 548				Study 549			
	Augmentin XR 2000/125mg b.i.d. N=313		Clarithro-mycin 500mg b.i.d. N=318		Augmentin XR 2000/125mg b.i.d. N=331		Levo-floxacin 500mg qd N=340	
Age (yrs)								
Mean (SD)	56.3 (12.1)		55.9 (12.0)		61.5 (12.1)		60.4 (12.0)	
Range	38-86		39-91		39-91		37-92	
Gender, n (%)								
Male	132	(42.2)	147	(46.2)	200	(60.4)	192	(56.5)
Female	181	(57.8)	171	(53.8)	131	(39.6)	148	(43.5)
Race: n (%)								
White	260	(83.1)	273	(85.8)	300	(90.6)	308	(90.6)
Black	41	(13.1)	37	(11.6)	26	(7.9)	26	(7.6)
Oriental	1	(0.3)	0	0	1	(0.3)	2	(0.6)
Other*	11	(3.5)	8	(2.5)	4	(1.2)	4	(1.2)
Smoking Pack Years, n (%)								
0	68	(21.7)	79	(24.8)	78	(23.6)	88	(25.9)
>0-10	54	(17.3)	44	(13.8)	27	(8.2)	27	(7.9)
>10-20	52	(16.6)	34	(10.7)	43	(13.0)	41	(12.1)
>20-30	37	(11.8)	40	(12.6)	65	(19.6)	60	(17.6)
>30	102	(32.6)	119	(37.4)	116	(35.0)	123	(36.2)
Unknown	0	-	2	(0.6)	2	(0.6)	1	(0.3)
Duration of (yrs)								
Mean (SD)	12.4 (11.7)		13.6 (11.7)		11.8 (9.7)		12.2 (9.6)	
Range	1.4-68.1		2.0-54.3		1.6-57.0		2.0-59.9	
No. of Exacerbations in Last Year Treated with Antibacterials, n (%)								
0	59	(18.8)	58	(18.2)	39	(11.8)	30	(8.8)
1-4	228	(72.8)	237	(74.5)	256	(77.3)	268	(78.8)
>4	26	(8.3)	23	(7.2)	35	(10.6)	38	(11.2)
Unknown	0	-	0	-	1	(0.3)	4	(1.2)
% Predicted Baseline FEV1, n (%)**								
<50%	59	(18.8)	60	(18.9)	90	(27.2)	76	(22.4)
50-70%	72	(23.0)	72	(22.6)	92	(27.8)	100	(29.4)
>70%	132	(42.2)	142	(44.7)	111	(33.5)	122	(35.9)
Unknown	50	(16.0)	44	(13.8)	38	(11.5)	42	(12.4)
Used Corticosteroids in Last Year, n (%)								
Yes	50	(16.0)	60	(18.9)	76	(23.0)	79	(23.2)

* Other races, as recorded verbatim by the investigator, were in Study 548, Hispanic (15 patients) and Italian-American, Guyana-Indian, Middle Eastern and Native American/German (one patient each); in Study 549, were North African (2 patients), Hispanic (2 patients) and Arab, Spanish, and Indian/Asian (1 patient each).
** Either derived from an FEV1 measurement taken on or between 6 days and 12 months prior to screening or derived from a measurement taken at or between end of therapy and long-term follow-up (not during an exacerbation)

Current smokers formed 46.4% of the Study 548 ITT population and 42.3% of the Study 549 ITT population. In Study 548, approximately 19% of patients in both treatment groups had severe airflow limitation, as evidenced by a reduction in FEV1 measurement to less than 50% of predicted. Similar proportions were seen

for the Clinical PP population in this study. In Study 549, there was a slightly higher proportion of patients with severe airflow limitation in the Augmentin XR group compared with the levofloxacin group (in the ITT population 27.2% of the Augmentin XR versus 22.4% of the levofloxacin group had baseline FEV1 <50% of predicted level; the corresponding proportions for the Clinical PP population were 28.0% in the Augmentin XR group and 21.9% in the levofloxacin group).

Use of systemic corticosteroids in the last year for pulmonary disease was higher in Study 549 compared with Study 548 (23.1% versus 17.4%, ITT population). Again similar observations were made for the Clinical PP population.

In the ITT population, only two patients in the Augmentin XR group and three patients in the levofloxacin group of Study 549 were hospitalized at screening for treatment of the presenting episode of —— No patients received in-patient treatment in Study 548.

In both studies at screening, the two treatment groups were well matched with respect to the clinical evaluation of the current episode of —— All patients had increased volume of purulent sputum at screening, together with increased cough and increased dyspnea, in accordance with the inclusion criteria for the study. In the ITT population of each study, more than 90% of patients in each treatment group had cough of at least moderate severity and more than 70% of patients in each treatment group had dyspnea of at least moderate severity.

Bacteriology at Screening

Sputum samples for bacteriological evaluation were collected at screening and where possible at end of therapy and test of cure. Sputum samples were assessed by microscopy to determine evaluable samples for culture, defined as >25 WBC per field and <10 squamous epithelial cells per field at 100x magnification. In Study 548, 23% of the Augmentin XR group (72/313 patients) and 21.7% of the clarithromycin group (69/318 patients) had at least one pathogen isolated from an evaluable sputum sample at screening in the ITT population. The corresponding numbers in the ITT population of Study 549 were 29.0% of the Augmentin XR group (96/331 patients) and 28.2% of the levofloxacin group (96/340 patients).

Overall, the pathogens isolated were consistent with those expected in ——— ——— *H. influenzae* was the most frequent pathogen isolated overall in both studies in both Bacteriology ITT and Bacteriology PP populations. The majority of patients from whom *H. influenzae* was isolated presented with single pathogen infections. However there were some differences between the treatment groups in the baseline pathogen incidence. For example, considering the Bacteriology ITT populations, in the Augmentin XR group the incidence of *H. influenzae* (29.2%) was higher and the incidence of *H. parainfluenzae* (15.3%) was lower in comparison with the clarithromycin group (*H. influenzae*, 17.4%; *H. parainfluenzae*, 27.5%). In Study 549, of note was a higher incidence of *S. pneumoniae* in the Augmentin XR group (19.8%) compared with the levofloxacin group (12.5%).

Differences in the incidences of bacterial species were also noted between studies, for example, there was a higher proportion of patients with *S. pneumoniae* in the Augmentin XR group of Study 549 in both Bacteriology ITT and Bacteriology PP populations (19.8% and 18.8%) in comparison with Study 548 (11.1% and 9.6%). A lower proportion of patients with *H. influenzae* was seen in both the Bacteriology ITT and Bacteriology PP populations of the clarithromycin group of Study 548 (17.4% and 17.9%, respectively), compared to the levofloxacin group of Study 549 (36.5% and 32.4%, respectively).

A summary of the most frequent pathogens associated with —— at screening in each of the principal studies is presented in the following table.

Number (%) of Patients with Key Pathogens Associated with — at Screening: — Principal Controlled Studies 548 and 549 (Bacteriology PP Test of Cure and Bacteriology ITT Populations)

	Study 548				Study 549			
Population	**Augmentin XR 2000/125mg b.i.d.**		**Clarithromycin 500mg b.i.d.**		**Augmentin XR 2000/125mg b.i.d.**		**Levofloxacin 500mg qd**	
Bacteriology PP*	**N=52**		**N=56**		**N=80**		**N=74**	
Total *H. influenzae*	17	(32.7)	10	(17.9)	27	(33.8)	24	(32.4)
Single pathogen *H. influenzae*	11	(21.2)	6	(10.7)	19	(23.8)	20	(27.0)
Total *H. parainfluenzae*	9	(17.3)	16	(28.6)	20	(25.0)	17	(23.0)
Single pathogen *H. parainfluenzae*	7	(13.5)	12	(21.4)	11	(13.8)	11	(14.9)
Total *M. catarrhalis*	9	(17.3)	12	(21.4)	14	(17.5)	12	(16.2)
Single pathogen *M. catarrhalis*	6	(11.5)	9	(16.1)	6	(7.5)	8	(10.8)
Total *S. pneumoniae*	5	(9.6))	9	(16.1)	15	(18.8)	8	(10.8)
Single pathogen *S. pneumoniae*	2	(3.8)	7	(12.5)	9	(11.3)	3	(4.1)
Total MSSA	8	(15.4)	10	(17.9)	9	(11.3)	10	(13.5)
Single pathogen MSSA	5	(9.6)	7	(12.5)	6	(7.5)	5	(6.8)
Bacteriology ITT*	**N=72**		**N=69**		**N=96**		**N=96**	
Total *H. influenzae*	21	(29.2)	12	(17.4)	29	(30.2)	35	(36.5)
Single pathogen *H. influenzae*	15	(20.8)	7	(10.1)	21	(21.9)	29	(30.2)
Total *H. parainfluenzae*	11	(15.3)	19	(27.5)	24	(25.0)	20	(20.8)
Single pathogen *H. parainfluenzae*	8	(11.1)	15	(21.7)	14	(14.6)	12	(12.5)
Total *M. catarrhalis*	11	(15.3)	14	(20.3)	18	(18.8)	15	(15.6)
Single pathogen *M. catarrhalis*	6	(8.3)	11	(15.9)	9	(9.4)	8	(8.3)
Total *S. pneumoniae*	8	(11.1)	10	(14.5)	19	(19.8)	12	(12.5)
Single pathogen *S. pneumoniae*	4	(5.6)	8	(11.6)	13	(13.5)	4	(4.2)
Total MSSA	13	(18.1)	12	(17.4)	10	(10.4)	15	(15.6)
Single pathogen MSSA	7	(9.7)	9	(13.0)	7	(7.3)	9	(9.4)

Notes: some patients had more than one pathogen at screening.

* There were many patients whose etiologic organism was uncommon (only one or two patients in the study with this particular organism isolated). These patients are not listed by organism in the table above but they are included in the totals.

The susceptibility (in terms of MIC and % susceptible, intermediate and resistant) of the key pathogens (*H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*,*S. p neumoniae* and MSSA) was determined against a panel of antibacterial agents. *Haemophilus spp*, *M. catarrhalis*, *Enterococcus spp*, and *S. aureus* were tested for beta-lactamase production.

In Study 548, the majority of isolates of the key pathogens tested (*H. influenzae*, MSSA, *H. parainfluenzae* and *S. pneumoniae*) were susceptible to both amoxicillin/clavulanic acid and the comparator clarithromycin, based on breakpoints defined by the NCCLS 2000. In Study 549, all screening isolates of the key pathogens tested (*H. influenzae*,*H. pa rainfluenzae*,*S. p neumoniae* and MSSA) were susceptible to amoxicillin/clavulanic acid, and to the comparator levofloxacin, based on NCCLS 2000 breakpoints. There are no NCCLS interpretations for *M. catarrhalis*; however, both Augmentin XR and the comparator regimens had good *in vitro* activity against this organism. In Study 548, for all *M. catarrhalis* pathogens, amoxicillin/clavulanic acid and clarithromycin MICs were ≤0.25µg/mL. In Study 549 for all *M. catarrhalis* pathogens, amoxicillin/clavulanic acid and levofloxacin MICs were ≤0.25µg/mL and ≤0.06µg/mL, respectively.

In Study 548, in the Bacteriology ITT population at screening for the 2 treatment groups combined, 3 isolates of *S. pneumoniae* (16.7%) were resistant to penicillin (penicillin MIC ≥ 2µg/mL according to NCCLS 2000 guidelines) and 4 isolates (22.2%) were resistant to macrolides (erythromycin MIC ≥ 1µg/mL according to NCCLS 2000 guidelines). Beta-lactamase production was detected in 9 isolates of *H. influenzae* (27.3%), 4 isolates of *H. parainfluenzae* (13.3%), 24 isolates of *M. catarrhalis* (96.0%) and 19 isolates of MSSA (76.0%).

In Study 549, in the Bacteriology ITT population at screening for the 2 treatment groups combined, 2 isolates of *S. pneumoniae* (6.5%) were resistant to penicillin and 7 isolates were resistant to erythromycin (22.6%). Beta-lactamase production was detected in 11 isolates *H. influenzae* (17.2%), 4 isolates of *H. parainfluenzae* (9.1%), 30 isolates of *M. catarrhalis* (90.9%) and 14 isolates of MSSA (53.8%).

A summary of the number of patients with key resistant pathogens in each of the principal studies is presented in the following table.

Number (%) Patients with Resistant Pathogens at Screening: Principal Controlled Studies 548 and 549 (Bacteriology ITT Population)

Bacteriology ITT	Study 548				Study 549			
	Augmentin XR N=72		Clarithromycin N=69		Augmentin XR N=96		Levofloxacin N=96	
	n/N	(%)	*n/N*	(%)	*n/N*	(%)	*n/N*	(%)
Penicillin-resistant *S. pneumoniae**	2/8	(25.0)	1/10	(10.0)	1/19	(5.3)	1/12	(8.3)
Erythromycin Resistant *S. pneumoniae***	1/8	(12.5)	3/10	(30.0)	5/19	(26.3)	2/12	(16.7)
Beta-Lactamase (+) *H. influenzae*	6/21	(28.6)	3/12	(25.0)	6/29	(20.7)	5/35	(14.3)
Beta-Lactamase (+) *H. parainfluenzae*	3/11	(27.3)	1/19	(5.3)	2/24	(8.3)	2/20	(10.0)
Beta-Lactamase (+) *M. catarrhalis*	11/11	(100.0)	13/14	(92.9)	15/18	(83.3)	15/15	(100.0)
Beta-Lactamase (+) MSSA	10/13	(76.9)	9/12	(75.0)	6/10	(60.0)	8/16	(50.0)

* Penicillin resistance defined as penicillin MIC of ≥2µg/mL.

** Erythromycin resistance defined as erythromycin MIC of ≥1µg/mL.

Note: *n/N* = number of resistant isolates/number of isolates of pathogens tested. If a patient had more than one isolate of a specified pathogen with MIC or beta-lactamase data, each of the isolates has been included.

Efficacy Results of Principal Controlled Studies

Primary Efficacy Variable

The primary efficacy variable in both principal studies was the clinical response (success or failure) at test of cure (Day 14-23). The proportion of patients with a clinical response of success or failure, together with the treatment differences and 95% CIs for the Clinical PP and ITT populations are presented in the table below.

The results of the two studies clearly demonstrate that the clinical response at test of cure to Augmentin XR 2000/125mg b.i.d. for 7 days was comparable to the response for the two comparators. In both studies, the analyses of the Clinical PP and ITT populations at test of cure demonstrated that the lower limit of the 95% CI for the difference in success rates (Augmentin XR minus comparator) was no less than the tolerable limit set for non-inferiority (-10%).

For the Clinical PP population, the proportion of patients who were clinical successes at test of cure were 83.4% for Augmentin XR compared with 86.2% for clarithromycin in Study 548, and 85.5% for Augmentin XR compared with 87.3% for levofloxacin in Study 549. There were slightly lower response rates overall in the ITT analyses in both studies. The small differences between the two analysis populations are mostly accounted for by the patients with a clinical outcome of Unable to Determine that were included as clinical failures in analysis of the ITT population and who were excluded from the Clinical PP population at test of cure.

An 'observed case' analysis of the ITT population from each study was also conducted to assess the sensitivity of the results to the classification of missing data. All patients with a clinical outcome of Unable to Determine were excluded from this analysis. In the observed case ITT population, the clinical success rates at test of cure were 83.9% in the Augmentin XR group and 85.8% in the clarithromycin group of Study 548 (treatment

difference: -1.9%; 95% CI: -7.6, 3.9), and 85.9% in the Augmentin XR group and 86.4% in the levofloxacin group of Study 549 (treatment difference: -0.5%; 95% CI: -6.0, 4.9). The results from the observed case ITT analysis in both studies were therefore consistent with the results of the PP analysis.

Clinical Response at Test of Cure: — Principal Controlled Studies 548 and 549 (Clinical PP and ITT Populations)

	Study 548				Study 549			
	Augmentin XR 2000/125mg b.i.d.		Clarithromycin 500mg b.i.d.		Augmentin XR 2000/125mg b.i.d.		Levofloxacin 500mg qd	
Clinical PP								
N	241		260		275		283	
Success, n (%)	201	(83.4)	224	(86.2)	235	(85.5)	247	(87.3)
Failure, n(%)	40	(16.6)	36	(13.8)	40	(14.5)	36	(12.7)
Clinical Failure at End of Therapy, n (%)	26	(10.8)	23	(8.8)	17	(6.2)	20	(7.1)
Clinical Recurrence, n (%)	14	(5.8)	13	(5.0)	23	(8.4)	16	(5.7)
Treatment Difference, %*	-2.8				-1.8			
95% CI	-9.1, 3.5				-7.5, 3.9			
ITT								
N	313		318		331		340	
Success, n (%)	245	(78.3)	259	(81.4)	262	(79.2)	274	(80.6)
Failure, n (%)	68	(21.7)	59	(18.6)	69	(20.8)	66	(19.4)
Clinical Failure at End of Therapy, n (%)	32	(10.2)	28	(8.8)	20	(6.0)	26	(7.6)
Clinical Recurrence, n (%)	15	(4.8)	15	(4.7)	23	(6.9)	17	(5.0)
Unable to Determine, n (%)	21	(6.7)	16	(5.0)	26	(7.9)	23	(6.8)
Treatment Difference, %*	-3.2				-1.4			
95% CI	-9.4, 3.1				-7.5, 4.6			

* Augmentin XR minus comparator

Additional efficacy data for Augmentin XR was provided by the sponsor in an analysis in which the primary efficacy variable data were combined from the two principal — studies. The clinical success rate at test of cure for the pooled Augmentin XR group was as good as the clinical success rate at test of cure for the combined active comparator group. The proportion of patients with clinical success was 84.5% for the combined Augmentin XR group compared with 86.7% for the combined comparator group in the Clinical PP population (treatment difference: -2.3%, 95% CI: -6.5, 2.0). The corresponding results for the ITT population were 78.7% for the combined Augmentin XR group compared with 81.0% for the combined comparator group (treatment difference: -2.3%, 95% CI: -6.6, 2.1).

In both individual — studies, a logistic regression analysis was performed to determine whether the treatment effect was consistent across different levels of covariates. The covariates tested were based on data for FEV1, cigarette smoking, frequency of treated exacerbations and previous systemic corticosteroid use; country was also included in Study 549. There were no statistically significant interactions between the covariates and treatment in either study with one exception. In Study 549, there was a statistically significant interaction between treatment and use of prior corticosteroids ($P<0.01$). Among patients that received previous corticosteroids, the treatment difference favored levofloxacin. This data could indicate the lower efficacy of Augmentin XR in this category of more severe patients, however, the same effect was not observed in Study 548; clinical success rates for the Augmentin XR group were similar between patients who had received corticosteroids and those who had not (Clinical PP: 82.1% and 83.7%, respectively). Also, the results are not consistent with the other indicators of severity tested in the logistic regression analysis of Study 549; FEV1 and frequency of treated exacerbations.

Secondary Efficacy Variables

Clinical Response at End of Therapy

Rates of clinical success at end of therapy were high in the two principal studies and consistent between the treatment groups. In Study 548 in the Clinical PP population, 89.7% of the Augmentin XR group and 91.4%

of the clarithromycin group were clinical successes at end of therapy. For the ITT population, clinical success rates were 85.3% and 87.7% for the Augmentin XR and clarithromycin groups, respectively. In Study 549, the clinical success rate at end of therapy in the Clinical PP population was 93.9% in the Augmentin XR group and 93.1% in the levofloxacin group. In the ITT population, clinical success rate at the end of therapy was 87.9% in the Augmentin XR group and 87.4% in the levofloxacin group.

Although the studies were not designed to demonstrate non-inferiority for secondary endpoints, in both studies and for both populations, the lower limits of the 95% CI for the treatment difference (Augmentin XR – comparator) were no less than the tolerability limit set for non-inferiority (–10%).

Bacteriological Response at Test of Cure and End of Therapy
The studies were not designed to demonstrate non-inferiority for secondary efficacy variables and the small numbers of patients in the bacteriological response analyses do not allow conclusions to be drawn from the results.

At test of cure in Study 548, the bacteriological success rates for the Bacteriology PP population were 73.1% in the Augmentin XR group and 83.9% in the clarithromycin group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 62.5% in the Augmentin XR group and 76.8% in the clarithromycin group. In Study 549, the bacteriological success rates at test of cure for the Bacteriology PP population were 78.8% in the Augmentin XR group and 83.8% in the levofloxacin group. In the Bacteriology ITT population, the bacteriological success rates at test of cure were 72.9% in the Augmentin XR group and 74.0% in the levofloxacin group. Bacteriological failure in many cases was due to the appearance of new pathogens rather than persistence of initial pathogens.

At end of therapy in Study 548, the bacteriological success rates for the Bacteriology PP population were 82.0% in the Augmentin XR group and 89.7% in the clarithromycin group. In the Bacteriology ITT population, the bacteriological success rates at end of therapy were 76.4% in the Augmentin XR group and 85.5% in the clarithromycin group. In Study 549, rates of bacteriological success at end of therapy were high and consistent between the treatment groups (Bacteriology PP: 92.8% Augmentin XR and 89.0% levofloxacin; Bacteriology ITT: 88.5% Augmentin XR and 84.4% levofloxacin).

Results of Eradication of Key Pathogens in —— Studies
The overall eradication of key pathogens associated with —— (combined pathogen outcomes of eradication and presumed eradication), has been assessed by pooling data from the two principal controlled —— studies at test of cure and end of therapy.

In the majority of patients, it was not possible to bacteriologically confirm the eradication of screening pathogens since repeat sputum samples could not be provided due to clinical improvement. As a result, only a small number of pathogens were documented as eradicated: 9.8% (17/173) of pathogens from Augmentin XR patients and 6.1% (10/164) of pathogens from the pooled comparator group patients in the Bacteriology PP population at test of cure.

In the following table, the overall eradication of pathogens for the pooled Augmentin XR group are compared with the overall eradication of pathogens for the pooled comparator group. For patients with more than one type of pathogen, each pathogen is included in the count for each individual micro-organism. However, if the patient had more than one isolate of the same pathogen, they are counted only once for that pathogen.

Number (%) Patients with Bacteriological Outcome of Eradicated or Presumed Eradicated by Pre-Therapy Pathogen: Combined — Studies 548 and 549 (Bacteriology PP and Bacteriology ITT Populations)

	Combined — studies 548 and 549							
	Bacteriology PP**				Bacteriology ITT			
Test of Cure	Augmentin XR N=132		All Comparators N=130		Augmentin XR N=168		All Comparators N=165	
	*n/N**	(%)	*n/N**	(%)	*n/N**	(%)	*n/N**	(%)
All Pathogens	139/173	(80.3)	132/164	(80.5)	157/220	(71.4)	151/209	(72.2)
H. influenzae	35/44	(79.5)	30/34	(88.2)	36/50	(72.0)	37/47	(78.7)
H. parainfluenzae	20/29	(69.0)	31/33	(93.9)	23/35	(65.7)	35/39	(89.7)
M. catarrhalis	19/23	(82.6)	22/24	(91.7)	20/29	(69.0)	24/29	(82.8)
S. pneumoniae	18/20	(90.0)	14/17	(82.4)	21/27	(77.8)	16/22	(72.7)
MSSA	16/17	(94.1)	14/20	(70.0)	19/23	(82.6)	14/27	(51.9)
	Bacteriology PP**				Bacteriology ITT			
End of Therapy	Augmentin XR N=144		All Comparators N=140		Augmentin XR N=168		All Comparators N=165	
	*n/N**	%	*n/N**	%	*n/N**	%	*n/N**	%
All Pathogens	175/189	(92.6)	159/178	(89.3)	193/220	(87.7)	175/209	(83.7)
H. influenzae	42/47	(89.4)	35/39	(89.7)	42/50	(84.0)	41/47	(87.2)
H. parainfluenzae	31/32	(96.9)	35/37	(94.6)	32/35	(91.4)	36/39	(92.3)
M. catarrhalis	24/26	(92.3)	24/25	(96.0)	26/29	(89.7)	25/29	(86.2)
S. pneumoniae	21/21	(100.0)	17/18	(94.4)	26/27	(96.3)	18/22	(81.8)
MSSA	16/17	(94.1)	17/21	(81.0)	20/23	(87.0)	20/27	(74.1)

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

** Data are for the Bacteriology PP population included in either the test of cure or end of therapy analyses.

Notes: 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.

At test of cure, the overall pathogen eradication rates were similar between the combined Augmentin XR group and the combined comparator group for both the Bacteriology PP and Bacteriology ITT populations (Bacteriology PP: Augmentin XR 80.3% versus comparators 80.5%; Bacteriology ITT: Augmentin XR 71.4% versus comparators 72.2%). The eradication/presumed eradication rates for each of the five key pathogens were all generally high, although some variations between the treatment groups were observed in both analysis populations. In particular, more *S. pneumoniae* and more MSSA were successfully eradicated in the combined Augmentin XR group compared with the combined comparator group. In contrast, in the combined comparator group the eradication rates were higher for *H. influenzae*, *H. parainfluenzae* and *M. catarrhalis* compared with the combined Augmentin XR group at test of cure. Of note, the eradication rate for *H. parainfluenzae* in the Augmentin XR group dropped from 96.9% (31/32) at end of therapy to 69.0% (20/29) at test of cure. In 6 cases this was due to the recurrence of *H. parainfluenzae* in patients who remained clinical successes at test of cure.

At end of therapy in the Bacteriology PP population, 92.6% of initial pathogens in the combined Augmentin XR group were either eradicated or presumed eradicated compared with 89.3% in the combined comparator group. The eradications rates for each of the five key pathogens were consistently high in both treatment groups. The results for the Bacteriology ITT population were similar to the Bacteriology PP population at this assessment.

In the Bacteriology PP population at test of cure, three patients in the Augmentin XR group and one patient in the combined comparator group had PRSP. All of the PRSP isolates demonstrated resistance to two or more classes of antibacterial agents. The three patients with PRSP (two of which were macrolide-resistant) in the Augmentin XR group were all clinical and bacteriological successes at test of cure (*S. pneumoniae* presumed

eradicated). The clarithromycin treated patient with a PRSP (also macrolide-resistant) was a clinical and bacteriological failure (presumed recurrence).

Four of 5 Augmentin XR patients with macrolide-resistant *S. pneumoniae* were a clinical and bacteriological success at test of cure; one Augmentin XR patient with macrolide-resistant *S. pneumoniae* was a clinical and bacteriological failure due to a superinfection with *M. catarrhalis* at end of therapy; the *S. pneumoniae* was eradicated at end of therapy but classified as unable to determine at test of cure. Two of 4 patients (50.0%) in the combined comparator group (PP population) had macrolide-resistant *S. pneumoniae* presumed eradicated at test of cure.

The majority of beta-lactamase producing strains of *H. influenzae,H. pa rainfluenzae,M. catarrhalis* and MSSA were eradicated (or presumed eradicated) in both the Bacteriology PP and Bacteriology ITT populations. In both the Bacteriology ITT and Bacteriology PP populations, the overall eradication rate of beta-lactamase positive MSSA was higher in the Augmentin XR compared with the combined comparator group. The overall eradication rates of beta-lactamase positive *M. catarrhalis* were higher in the combined comparator group compared with the Augmentin XR group. This was also true for *H. parainfluenzae.* However, the small numbers of these beta-lactamase producing organisms do not allow firm conclusions to be drawn about differences between treatment groups.

New Pathogens

In the Bacteriology PP and Bacteriology ITT populations for the combined Augmentin XR group, two patients had a new pathogen at test of cure; one new infection with *H. influenzae* and one colonization with *S. pneumoniae*. For the combined comparator group, two patients in the Bacteriology PP population had colonization (*K. pneumoniae* and MSSA, respectively) at test of cure. An additional patient in the Bacteriology ITT population of the combined comparator group had colonization with *S. pneumoniae*.

In the Bacteriology PP population, a total of 8 patients in the combined Augmentin XR group had new bacteria isolated at end of therapy (3 superinfections with one pathogen, 1 superinfection with 2 pathogens and 4 colonizations). In the Bacteriology ITT population, there were an additional 2 patients with superinfection and one with colonization. In the combined comparator group, there were 3 patients with new bacteria at end of therapy (1 superinfection and 2 colonizations) in both the Bacteriology PP and Bacteriology ITT populations.

Subgroup Analyses of —— Studies

In the pooled analysis of the —— studies, the effects of covariates (age, gender and race, systemic corticosteroid use for pulmonary disease in the previous 12 months, percent predicted FEV1 at baseline, cigarette smoking pack years and exacerbations treated with antibacterial agents in the previous 12 months) were formally investigated by logistic regression modelling.

In summary there was no evidence of significant interactions between treatment and age, gender, race, the number of antibacterial-treated exacerbations in the last 12 months, smoking pack years and percent predicted baseline FEV1. The regression modelling confirmed a significant interaction between treatment and the use of systemic corticosteroids for pulmonary disease during the past 12 months (P=0.06). The 95% CI for the treatment difference (Augmentin XR-comparators) for patients who had used corticosteroids was (-20.6%, 1.4%) and for the non-users group was (–5.1%, 3.9%). A statistically significant interaction between treatment and use of corticosteroids was observed in Study 549. The regression modelling for the pooled analysis also indicated that clinical responses overall were lower for patients with an FEV1 measurement of <50% compared to patients with FEV1 measurements of >70%, although no significant interaction with treatment was noted.

Demographic Characteristics

The clinical success rates for subgroups by age, gender and race demonstrated consistent rates between the major subgroups in both treatment groups and similar rates to the total combined study population. In particular, the clinical success rates were consistent between patients aged ≥65 years and 40-64 years and

between male and female patients. Although the majority of the patients were white (84.1% for Augmentin XR and 86.8% for All Comparators in Clinical PP test of cure population), the clinical success rates for the small number of black and patients of other races did not indicate any differential responses compared with the total study population.

Clinical Success Rates at Test of Cure by Demographic Subgroups:
Combined — Studies 548 and 549 (Clinical PP and ITT Populations)

	Combined — Studies 548 and 549							
	Clinical PP				ITT			
	Augmentin XR N=516		All Comparators N=543		Augmentin XR N=644		All Comparators N=658	
	*n/N** (%)		*n/N**	(%)	*n/N**	(%)	*n/N**	(%)
Age								
<40 years	3/3	(100.0)	4/4	(100.0)	6/6	(100.0)	4/4	(100.0)
40-64 years	274/326	(84.0)	307/362	(84.8)	326/413	(78.9)	356/446	(79.8)
≥65 years	159/187	(85.0)	160/177	(90.4)	175/225	(77.8)	173/208	(83.2)
Gender								
Male	230/274	(83.9)	245/281	(87.2)	263/332	(79.2)	273/339	(80.5)
Female	206/242	(85.1)	226/262	(86.3)	244/312	(78.2)	260/319	(81.5)
Race								
White	381/453	(84.1)	420/484	(86.8)	439/560	(78.4)	473/581	(81.4)
Black	45/52	(86.5)	42/48	(87.5)	54/67	(80.6)	51/63	(81.0)
Oriental	1/1	(100.0)	1/2	(50.0)	1/2	(50.0)	1/2	(50.0)
Other	9/10	(90.0)	8/9	(88.9)	13/15	(86.7)	8/12	(66.7)

* *n* = number of patients with a clinical response of success, *N* = number of patients included in the subgroup.

Clinical History Characteristics

Previous Corticosteroid Use:
The majority of patients had not taken systemic corticosteroids for pulmonary disease during the past 12 months (Augmentin XR: 81.6%; pooled comparators 79.7%, Clinical PP). The clinical success rate was lower for patients who had taken corticosteroids compared with patients who had not taken corticosteroids, an effect that was most noticeable in the Augmentin XR group. As discussed above, the regression modelling confirmed a significant interaction between treatment and previous systemic corticosteroid use (P=0.06). Further interpretation of this result is difficult since the results were not consistent with the other indicators of severity tested in the logistic regression analysis; FEV1 and frequency of treated exacerbations.

Clinical Success Rates at Test of Cure by Clinical History Subgroups:
Combined — Studies 548 and 549 (Clinical PP and ITT Populations)

	Combined — Studies 548 and 549							
	Clinical PP				ITT			
	Augmentin XR N=516		All Comparators N=543		Augmentin XR N=644		All Comparators N=658	
	*n/N**	%	*n/N**	(%)	*n/N**	(%)	*n/N**	(%)
Systemic Corticosteroid Use**								
Yes	71/95	(74.7)	93/110	(84.5)	89/126	(70.6)	107/139	(77.0)
No	365/421	(86.7)	378/433	(87.5)	418/518	(80.7)	426/519	(82.1)
% Predicted Baseline FEV1								
<50%	101/126	(80.2)	101/115	(87.8)	115/149	(77.2)	111/136	(81.6)
50-70%	124/138	(89.9)	136/150	(90.7)	140/164	(85.4)	151/172	(87.8)
>70%	185/202	(91.6)	212/229	(92.6)	221/243	(90.9)	239/264	(90.5)
Unknown	26/50	(52.0)	22/49	(44.9)	31/88	(35.2)	32/86	(37.2)
Cigarette Smoking Pack Years								
None	105/116	(90.5)	134/148	(90.5)	123/146	(84.2)	146/167	(87.4)
>0-10 years	57/64	(89.1)	41/50	(82.0)	66/81	(81.5)	55/71	(77.5)
>10-20 years	61/73	(83.6)	54/63	(85.7)	74/95	(77.9)	60/75	(80.0)
>20-30 years	70/82	(85.4)	65/76	(85.5)	82/102	(80.4)	76/100	(76.0)
>30 years	143/180	(79.4)	174/203	(85.7)	161/218	(73.9)	193/242	(79.8)
Unknown	0/1	(0.0)	3/3	(100.0)	1/2	(50.0)	3/3	(100.0)
Treated Exacerbations in Last 12 months §								
0	61/73	(83.6)	66/71	(93.0)	75/98	(76.5)	73/88	(83.0)
1–4	335/395	(84.8)	357/415	(86.0)	383/484	(79.1)	408/505	(80.8)
>4	39/47	(83.0)	45/54	(83.3)	48/61	(78.7)	48/61	(78.7)
Unknown	1/1	(100.0)	3/3	(100.0)	1/1	(100.0)	4/4	(100.0)

* *n* = number of patients with a clinical response of success, *N* = number of patients included in the subgroup.
** Use of systemic corticosteroids for pulmonary disease during the past 12 months.
§ Number of ——— treated with systemic antibacterials during the past 12 months.

Percent predicted Bas eline FEV1:
In both treatment groups (Clinical PP), the clinical success rates were slightly lower for patients with an FEV1 measurement of <50% (overall rate: 83.8%) com pared with patients with an FEV1 measurement of 50-70% (overall rate: 90.3%) and patients with an FEV1 measurement of >70% (overall rate: 92.1%). The results for the ITT population were similar.

Smoking Pack Years: In the Augmentin XR group (Clinical PP), the clinical success rates appeared slig htly lower for patients with a smoking history of >30 pack years (79.4%) compared with non-smokers (90.5%). However the results of the regression modeling did not confirm an effect of smoking history on clinical response rates. The results for the ITT population were similar.

Treated Exacerbations: Only a small proportion of patients had >4 exacerbations trea ted with antibacterials in the last 12 months (overall 9.5% in the Clinical PP population). The clinical success rates for subgroups based on the number of treated exacerbations in the last 12 months (Clinical PP and ITT), demonstrated consistent rates between the subgroups and similar rates compared with the total combined study population.

Efficacy of Augmentin XR in —— Discussion and Conclusions

Discussion
Two well-controlled, double-blind, parallel group principal studies have assessed the clinical and bacteriologic al efficacy of Augmentin XR 2000/125mg twice daily for 7 days in comparison with other antibiotics approved for the treatment of patients with ——

The results of the two studies demonstrate that the clinical response to Augmentin XR at test of cure (primary efficacy variable) was at least as good as the response for clarithromycin 500mg b.i.d. for 7 days and levofloxacin 500mg once daily for 7 days. In both studies, the analyses of the Clinical PP and ITT populations at test of cure demonstrated that the lower limit of the 95% CI for the difference in success rates (Augmentin XR comparator) was no less than the tolerable limit (-10%).

The clinical success rates at test of cure for Augmentin XR patients in Studies 548 and 549 (83.4% and 85.5%, respectively, for the Clinical PP populations) were within an acceptable range for treatment of this indication. The corresponding rates for the comparator groups in each of the studies were 86.2% (clarithromycin) and 87.3% (levofloxacin), respectively. The results of the primary clinical response analysis were also supported by high clinical success rates at the end of therapy assessment (89.7% and 93.9% for the Augmentin XR Clinical PP populations in Studies 548 and 549, respectively).

In terms of bacteriological response, the numbers of patients in the Bacteriology PP and Bacteriology ITT populations in both studies were too small to draw any definite conclusions on non-inferiority. The results at test of cure indicated lower bacteriological success rates in the Augmentin XR group in Study 548 compared with the clarithromycin group (Bacteriology PP: 73.1% vs 83.9%; Bacteriology ITT: 62.5% vs 76.8%) and similar success rates between the Augmentin XR and levofloxacin groups in Study 549 (Bacteriology PP: 78.8% vs 83.8%; Bacteriology ITT 72.9% vs 74.0%).

Summary of Clinical and Bacteriological Response at Test of Cure:
Principal Controlled Studies (All Populations)

	Success Rate		
	Augmentin XR % (n/N)	Comparator* % (n/N)	Treatment Difference % (95% CI)**
CLINICAL RESPONSE (PRIMARY PARAMETER)			
Clinical PP Population			
548	83.4% (201/241)	86.2% (224/260)	-2.8 (-9.1, 3.5)
549	85.5% (235/275)	87.3% (247/283)	-1.8 (-7.5, 3.9)
ITT Population			
548	78.3% (245/313)	81.4% (259/318)	-3.2 (-9.4, 3.1)
549	79.2% (262/331)	80.6% (274/340)	-1.4 (-7.5, 4.6)
BACTERIOLOGICAL RESPONSE			
Bacteriology PP Population			
548	73.1% (38/52)	83.9% (47/56)	-10.9 (-26.3, 4.6)
549	78.8% (63/80)	83.8% (62/74)	-5.0 (-17.3, 7.2)
ITT Population			
548	62.5% (45/72)	76.8% (53/69)	-14.3 (-29.3, 0.7)
549	72.9% (70/96)	74.0% (71/96)	-1.0 (-13.5, 11.5)

* Comparators were clarithromycin 500mg b.i.d. for 7 days in Study 548 and levofloxacin 500mg qd for 7 days in Study 549.

** Non-inferiority limit was prospectively defined as ≥-10% for Studies 548 and 549.

In the context of bacteriological response, the baseline pathogen profile differed between treatment groups, most noticeably in Study 548. In this study there was a higher incidence of *H. influenzae* (29.2%) in the Augmentin XR group compared with the clarithromycin group (17.4%) (Bacteriology ITT). In the clarithromycin group, *H. parainfluenzae* was the predominant pathogen (27.5%). Also, in Study 548, examination of treatment failures in the Bacteriology PP population at test of cure shows a higher proportion of clinically resolved patients with continued presence of pathogenic bacteria in cultures of sputum in the Augmentin XR group (6/14, 42.9%) compared with the clarithromycin group (2/9, 22.2%). These findings could be indicative of patients who are not experiencing an exacerbation, but are colonized with bacteria commonly associated with

In the combined — study population, the distribution of pathogens by species was consistent with that commonly associated with ~ the most frequently recovered pathogens were *H. influenzae*, *H. parainfluenzae*,*M. catarrhalis*, *S. pneumoniae* and MSSA. The overall pathogen eradication rates were consistent between the combined Augmentin XR group and the combined comparator group at test of cure (Bacteriology PP: Augmentin XR 80.3% vs. Comparators 80.5%; Bacteriology ITT: Augmentin XR 71.4% vs Comparators 72.2%). The eradication rates for each of the five key pathogens were all generally high, although some variations between treatments were observed. Of note, the eradication rate for *H. parainfluenzae* in the Augmentin XR group dropped from 96.9% (31/32) at end of therapy to 69.0% (20/29) at test of cure. In 6 cases this was due to the recurrence of *H. parainfluenzae* in patients who remained clinical successes at test of cure.

The pathogen eradication rates included isolates that showed evidence of resistance to antibacterial agents, including PRSP, macrolide-resistant *S. pneumoniae* and beta-lactamase producing strains of the key pathogens. In the Augmentin XR group, 3/3 (100%) patients with PRSP (penicillin MIC ≥2µg/mL) and 4/5 (80%) of patients with macrolide-resistant *S. pneumoniae* (Bacteriology PP populations) were clinical and bacteriological successes at test of cure.

Conclusions

The principal conclusions of the efficacy assessment of Augmentin XR in — are as follows:

- In two principal clinical studies, Studies 548 and 549, the efficacy of Augmentin XR 2000/125mg twice daily for 7 days was as good as that of clarithromycin 500mg b.i.d. for 7 days and levofloxacin 500mg once daily for 7 days, in terms of clinical response at test of cure (primary efficacy variable).

- In both Studies 548 and 549, the results for the primary efficacy variable were consistent between the Clinical PP and ITT populations.

- No significant interaction between treatment and age was identified in the covariate analysis. Furthermore, clinical success rates were consistent between patients aged ≥65 years and those aged 40-64 years.

- Augmentin XR successfully eradicated key pathogens associated with — namely, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *S. pneumoniae* and MSSA, including strains possessing resistance mechanisms.

These data support the indication of Augmentin XR (2000/125mg twice daily for 7 days) for the treatment of [ ]. However, there is no information in this application which indicates that this product offers any additional benefit when compared to the already approved Augmentin formulations. The issue of the potential advantage conferred by this product in the treatment of —— is not considered to be valid at this time. There is no current medical data which demonstrates the clinical significance of — in the treatment or outcome of ← The higher amount of amoxicillin contained in this formulation results in a higher rate of adverse events, such as diarrhea, but confers no additional efficacy over already approved formulations of Augmentin. This formulation can be expected to have an increased risk but no proven additional benefit. Therefore, the risk benefit analysis argues against approval because the already approved formulation of Augmentin provides the same benefit with a lower rate of adverse events.

INTEGRATED SUMMARY OF SAFETY

OVERVIEW

The Integrated Summary of Safety (ISS) for Augmentin XR consists of data from three completed clinical pharmacology studies (Study 553, Study 558 and Study 583), five completed, active-comparator, controlled clinical studies, one completed, uncontrolled study and the interim analysis of data up to 19 June 2000 from an ongoing, uncontrolled study. Two of the completed, controlled studies were conducted in patients with [redacted]; Study 548 and Study 549), two were conducted in patients with community acquired pneumonia (CAP; Study 546 and Study 556) and one was conducted in patients with acute bacterial sinusitis (ABS Study 550). Uncontrolled studies were conducted in patients with CAP (Ongoing Study 547, interim analysis) and ABS (Study 551).

In addition, this ISS contains a summary of deaths and serious adverse experiences (SAEs) as of the clinical data cut-off of 31 August 2000 from one ongoing, active-comparator, controlled study (Study 557) of patients with CAP. Deaths and SAEs that occurred after 19 June 2000 and before the clinical data cut-off of 31 August 2000 in the ongoing portion of CAP Study 547 are also reported.

On February 23, 2001 the Division requested a re-analysis of safety and efficacy results excluding patients enrolled by three investigators, Drs. C. Andrew DeAbate, W. Sokol, and C. P. Mathew. Data from these investigators were censored due to concerns about data integrity. At a teleconference with the Division on May 14, 2001 it was agreed that the sponsor would provide an abridged integrated summary of safety with patients enrolled by these investigators removed.

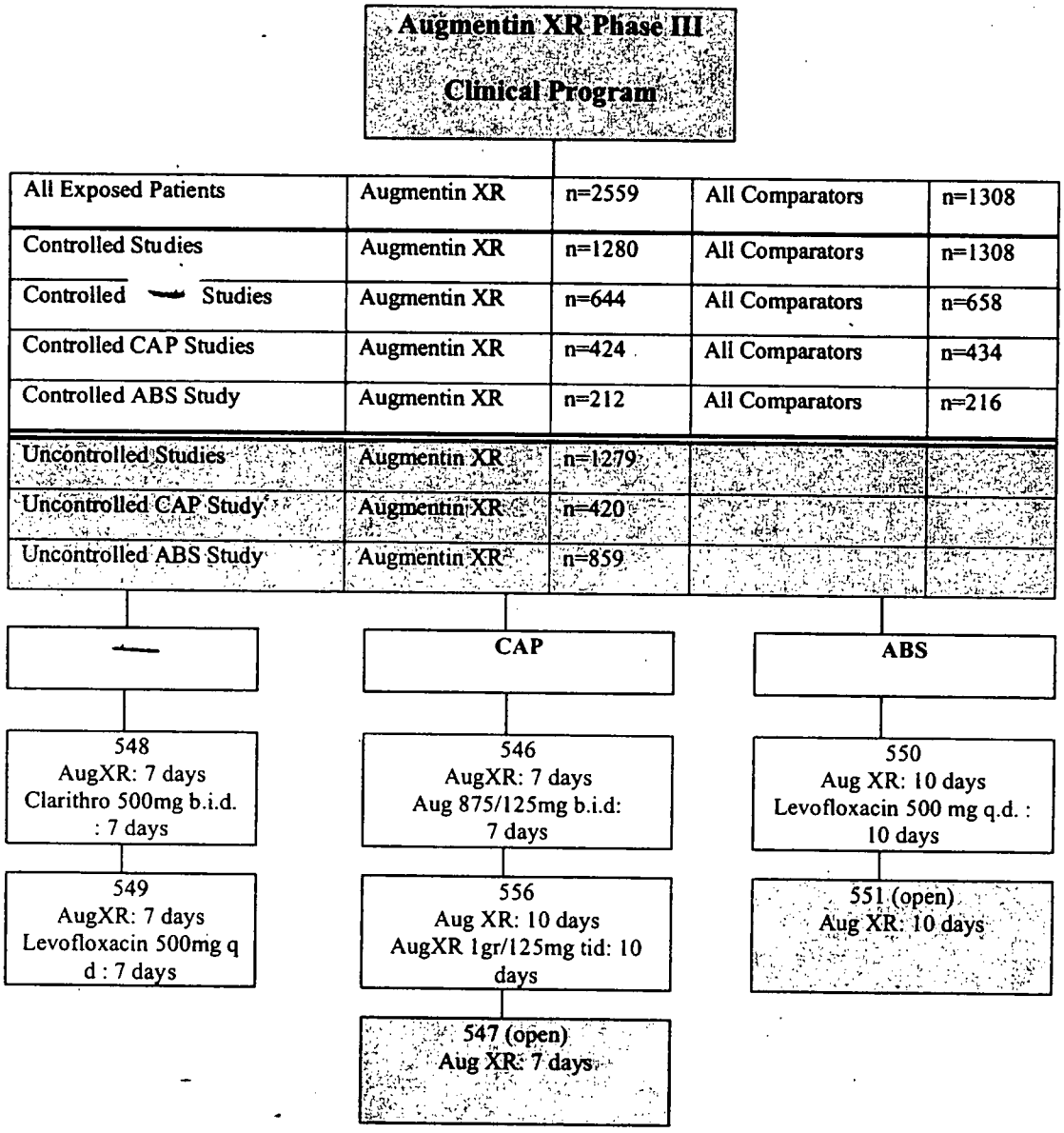
These investigators contributed a total of 235 patients to four studies in acute bacterial sinusitis (ABS studies 550 & 551) and [redacted] studies 548 & 549). Studies 548, 549 and 550 are controlled clinical studies, while study 551 is an open bacteriological study.

Number of Patients Enrolled by Dr. DeAbate, Dr. Sokol, and Dr. Mathew in Clinical Studies 548, 549, 550 and 551

Study	Dr. Sokol	Dr. DeAbate	Dr. Mathew	Total
	n/N, (%)	n/N, (%)	n/N, (%)	n/N, (%)
548	0/634	0/634	46/634 (7.3)	46/634 (7.3)
549	0/673	49/673 (7.3)	0/673	49/673 (7.3)
550	0/432	39/432 (9.0)	29/432 (6.9)	68/432 (15.8)
551	17/861 (2.0)	0/861	55/861 (6.4)	72/861 (8.4)
Total	17/2600 (0.7)	88/2600 (3.4)	130/2600 (5.0)	235/2600 (9.0)

This document presents the results of the safety re-analyses for the affected Phase III clinical studies (Studies 548, 549, 550 and 551) and integrated analyses that describe the safety of Augmentin XR. Investigators DeAbate, Sokol, and Mathew have been removed from the safety data presented here.

Summary of Phase III Clinical Program to Evaluate the Safety of Augmentin XR



* Study 547 includes safety data from an interim analysis of patients who completed the study on or before 19 June 2000 and whose data were received by SmithKline Beecham (SB). Patients who reported an SAE or whose SAE data were received after 19 June 2000 but prior to the clinical cut-off date of 31 August 2000 are included in Ongoing Studies, ISS Section.

Note: The dosage and frequency of Augmentin XR was 2000/125mg b.i.d. in all Phase III studies.

EXTENT OF EXPOSURE

Methodology

The safety population consisted of all patients who received at least one dose of study medication. Extent of exposure for each patient in the Phase III studies was calculated as follows:

Duration of treatment = (stop date - start date) + 1.

Therefore in a case where study medication started and stopped on the same day, study medication was considered to have been stopped on the first day of dosing and the duration of treatment was 1 day, although the medication was started and stopped on Day 0 relative to the date of first dose.

Where it was not possible to calculate the above, exposure was tabulated as unknown.

Patients frequently initiated therapy with the evening dose and thus took only one dose of study medication on Day 0. Therefore, exposures of 8 days in 7-day treatment studies and 11 days in 10-day treatment studies were common because the patient finished on the morning of the 8th or 11th day of dosing.

Pharmacology Studies

A total of 59 healthy subjects were enrolled into three clinical pharmacology studies. Fifty-five subjects received Augmentin XR at one or more dosing sessions (Study 558: 8 subjects, Study 553: 27 subjects, Study 583; 20 subjects). Twelve subjects were enrolled in Study 558. All twelve of these subjects received other formulations of Augmentin which were not progressed to Phase III studies and 8/12 subjects also received Augmentin XR in a cross-over design. Twenty seven subjects were enrolled in Study 553 all of whom received Augmentin XR. Twenty subjects were enrolled in Study 583 and all of these subjects received Augmentin XR alone and in combination with Maalox. All subjects received single doses of Augmentin XR or other formulations of Augmentin in each study session and the mean exposure was 3.1 days. No repeated doses of Augmentin XR or other Augmentin formulations were administered in these clinical pharmacology studies.

Clinical Studies

In the Phase III program, a total of 2423 patients received Augmentin XR and 1226 patients received comparators in five completed double-blind, active-comparator clinical studies and two uncontrolled, non-comparative clinical studies. The scheduled duration of treatment with Augmentin XR was either 7 days or 10 days, according to the study protocol.

Controlled Studies

In controlled studies, 1199 patients received Augmentin XR and 1226 received a comparator. The mean duration of exposure was 8.1 days in both the Augmentin XR group and the All Comparators group. The range of exposure was 1 to 22 days in the Augmentin XR group and 1 to 15 days in the All Comparators group.

Augmentin XR was taken for 7 or 8 days by 65.2% of patients and for 10 or 11 days by 26.0% of patients. Two patients had a duration of exposure to Augmentin XR of ≥15 days: 548.142.07399 (16 days), and 548.142.07396 (22 days). The investigators confirmed these extended durations and commented that no more than the maximum expected number of tablets were taken. In the All Comparators group, one patient (550.414.03545) had an exposure to levofloxacin of 15 days.

Extent of Exposure in Combined Controlled Studies

	Treatment Group			
	Augmentin XR		**All Comparators***	
Extent of Exposure (days)	**N= 1199**		**N= 1226**	
Mean (SD)	8.1 (2.0)		8.1 (1.9)	
Range	(1-22)		(1-15)	
Duration of Therapy (days)	**n**	**(%)**	**n**	**(%)**
1	12	1.0	5	0.4
2	14	1.2	15	1.2
3	15	1.3	13	1.1
4	18	1.5	19	1.5
5	11	0.9	10	0.8
6	6	0.5	7	0.6
7	435	36.3	474	38.7
8	347	28.9	329	26.8
9	8	0.7	10	0.8
10	113	9.4	142	11.6
11	199	16.6	185	15.1
>11	10	0.8	12	1.0
Unknown	11	0.9	5	0.4

*All Comparators were clarithromycin 500mg b.i.d. (N=295), levofloxacin 500mg qd (N=497), Augmentin 875/125 mg b.i.d. (N= 259) and Augmentin 1000/125mg t.i.d. (N=175)

Uncontrolled Studies

A total of 1224 patients received Augmentin XR in uncontrolled studies (Study 547: 7 day treatment duration, Study 551, 10 day treatment duration). The mean duration of exposure was 9.4 days, with a range of exposure of 1 to 19 days.

Augmentin XR was received for 7 or 8 days by 31.6% of patients and for 10 or 11 days by 61.4% of patients. One patient (547.209.08569) had an exposure to Augmentin XR of more than 15 days; dosing was interrupted due to hospitalization for worsening pneumonia.

Extent of Exposure in Combined Uncontrolled Studies

	Treatment Group	
	Augmentin XR	
Extent of Exposure (days)	**N=1224**	
Mean (SD)	9.4 (1.9)	
Range	(1-19)	
Duration of Therapy (days)	**n**	**(%)**
-1	8	0.7
2	6	0.5
3	7	0.6
4	7	0.6
5	8	0.7
6	7	0.6
7	163	13.3
8	224	18.3
9	7	0.6
10	331	27.0
11	421	34.4
>11	21	1.7
Unknown	14	1.1

Extent of exposure is also presented by indication because the treatment duration varied with the indication under study.

In the — studies the mean duration of exposure was 7.2 days in both the Augmentin XR group and the All Comparators (levofloxacin or clarithromycin) group. The mean duration of exposure in the controlled CAP studies was 8.3 days in the Augmentin XR group and 8.4 days in the All Comparators (Augmentin 875/125mg or Augmentin 1000/125mg) group. In uncontrolled CAP Study 547 (interim analysis up to 19 June 2000), the mean duration was 7.4 days, reflecting the 7-day treatment period. The mean duration of exposure in controlled ABS Study 550 was 10.3 days for Augmentin XR and 10.4 days for levofloxacin. Similarly, mean duration of exposure in uncontrolled ABS Study 551 was 10.4 days.

Demography

Pharmacology Studies
Fifty-nine percent of subjects in the three clinical pharmacology studies were female. Ninety-seven percent were white. All of the healthy subjects enrolled into clinical pharmacology studies were aged less than 60 years. The mean age of the total volunteer population was 34.5 years (range 18 years to 58 years) with a mean weight of 68.4 kg (range 51 kg to 86 kg).

Clinical Studies
In the Phase III program, 2423 patients were treated with Augmentin XR and 1226 patients with comparators. The distribution of patients in the controlled and uncontrolled studies by gender was generally even in the Augmentin XR and All Comparator groups; the majority of patients were white (82.4% in the Augmentin XR group, 86.4% in the All Comparators group). The mean age of patients who received Augmentin XR in the controlled and uncontrolled studies was 49 years, with a range of 16 to 93 years. Among Augmentin XR-treated patients in controlled and uncontrolled studies, 20.8% were ≥65 years old and 8.1% were ≥75 years old. The mean age of patients who received comparator was 54.6 years, with a range of 16 to 92 years; 29.4% were ≥65 years old and 11.8% were ≥75 years old. The distribution of Augmentin XR-treated patients in the controlled and uncontrolled studies by country was 52.7% from the United States, 40.9% from Europe and 6.4% from other countries.