and lower than the overall rate for CAP (9%) in the literature[1]. Of the deaths in Augmentin XR patients, only three occurred on therapy. One patient died due to pulmonary tuberculosis. The second was a sudden cardiac event in an elderly male with a history of heart disease. The third was in a 45-year old male with history of alcohol abuse with psychiatric disease whose death occurred one day after the last dose of Augmentin XR. His death was due to cerebral vascular accident (CVA). There were 2 deaths due to CVA, one in controlled study (45-year old alcoholic male) and the other in the uncontrolled study (69-year old male with diabetes mellitus, ischemic heart disease and uncontrolled hypertension). In reviewing the submitted NDA datasets and published literature, there did not seem to be any increased reports of clotting problems or bleeding disorders in patients treated with Augmentin products. The majority of deaths were not temporally associated with treatment and were clearly related to other causes (most related to cancer).
About 81% of patients who died were ≥ 65 years of age (mean age for all patients was 69.5 years). All the patients had either one or more comorbid conditions. There were 3 patients who died who were less than 50 years old – one was an alcoholic, one had HIV infection and one had adenocarcinoma of the lung. None of the patients that died had resistant pathogens isolated, and none of them had hepatic dysfunction. Most of the deaths occurred after study drug therapy had been completed. Based on the review, the medical officer concurs with the applicant's conclusions.

Serious Adverse Experiences

Summary

Of the 4144 patients who received Augmentin XR in Phase 3 studies, 3.5% (143 patients) reported at least one SAE during the interval on-therapy to within 30 days post-therapy. Of the 1387 patients in the All Comparators group, 5.2% (72 patients) reported SAEs during this period. The proportion of patients who had SAEs reported on-therapy or within 30 days post-therapy was slightly higher among patients who received Augmentin XR in the 6 completed controlled studies (60/1357- 4.4%) compared with the proportions in the 3 completed uncontrolled studies (83/2787 - 3.0%) and among all exposed patients (143/4144 - 3.5%). However, similar SAE profiles were observed among patients who received Augmentin XR in the combined controlled studies and combined uncontrolled studies, and among all patients exposed.
In more than 90% of all patients exposed in both treatment groups, SAEs were considered by the investigators to be unrelated or of unlikely relationship to the study medication. The most frequently reported (approximately 1.0%) SAE in both treatment groups was pneumonia. Reports of pneumonia were generally associated with worsening or recurrence of baseline pneumonia and were reported primarily among patients enrolled in CAP studies. Small proportions of patients had SAEs associated with the gastrointestinal body system reported on-therapy or within 30 days post-therapy; diarrhea was reported as an SAE in 2 patients in the Augmentin XR group and no patients in the All Comparators group.

[1] Mortensen EM et al., "Causes of Death for Patients with Community-Acquired Pneumonia" *Arch Intern Med* 162(9):1059-1064 May 13, 2002

The rate for Augmentin XR was similar to that observed for All Comparators in all three datasets in the controlled studies; 4.4%, 10.8%, and 3.6% of patients in the Augmentin XR group and 5.2%, 11.2%, and 4.4% of patients who received comparator medications reported SAEs on-therapy or within 30 days post-therapy in the combined, new, and NDA datasets, respectively. Pneumonia was the most frequently reported SAE among patients who received Augmentin XR and comparators in all three datasets.

A comparison of SAE for Augmentin XR versus the currently approved Augmentin treatment regimen (Augmentin 875/125-mg b.i.d.) was made in the CAP study 546. During the interval on-therapy to within 30 days post-therapy, SAEs occurred in 5.9% (15/255) of patients in the Augmentin XR group and in 7.3% (19/259) of patients in the Augmentin 875/125mg group. The only SAEs reported in more than one patient in the Augmentin XR group were pneumonia in 1.2% (3/255) of patients and pulmonary carcinoma in 0.8% (2/255) of patients. In the Augmentin 875/125mg group, the only SAEs reported in more than one patient were pneumonia in 1.5% (4/259) of patients, cardiac failure and therapeutic response increased (i.e., overdose) each in 1.2% (3/259) of patients, and pleural effusion in 0.8% (2/259) of patients.

Withdrawals Due to Adverse Experiences

Summary

The proportion of patients reporting adverse experiences (AEs) leading to withdrawal during the interval on-therapy to within 30 days post-therapy was similar in the Augmentin XR group (3.9%) and the All Comparators (4.5%) group among all patients exposed to study medication in the Phase 3 clinical program. The most frequently reported AEs leading to withdrawal were diarrhea and pneumonia, each reported in less than 1.0% of patients in either treatment group. Reports of pneumonia were generally associated with worsening or recurrence of baseline pneumonia and were reported primarily among patients enrolled in CAP studies. Withdrawal due to AEs associated with the gastrointestinal body system were reported on-therapy or within 30 days post-therapy in approximately 1.5% of patients in both treatment groups.

The proportions of patients with an AE leading to withdrawal reported on-therapy or within 30 days post-therapy were similar among all patients who received Augmentin XR in the new, original NDA, and combined (NDA and new studies) datasets. In the controlled and uncontrolled studies, the proportion of patients with AEs leading to withdrawal in the new dataset was generally higher among patients who received Augmentin XR than in the original NDA or combined datasets; the most pronounced difference occurred in the new dataset in the controlled population. However, the rate for Augmentin XR was similar to that observed for comparators in all three datasets in the controlled studies.

The proportion of patients who had AEs leading to withdrawal reported on-therapy or within 30 days post-therapy was slightly higher among patients who received Augmentin

XR in the 6 controlled studies (4.7%) compared with the proportions in the 3 uncontrolled studies (3.4%) and among all exposed patients (3.9%). However, similar AE profiles were observed among patients who received Augmentin XR in the combined controlled studies and combined uncontrolled studies, and among all patients exposed.

A comparison of Augmentin XR versus the conventional Augmentin treatment regimen (Augmentin 875/125mg bid) in CAP Study 546 showed a lower proportion of patients with AEs leading to withdrawal during the interval on-therapy to within 30 days post-therapy among patients who received Augmentin XR [3.5% (9/255) of patients in the Augmentin XR group and 6.9% (18/259) of patients in the Augmentin 875/125mg group].

Proportions of patients with AEs or SAEs of suspected or probable relationship to the study medication leading to withdrawal were comparable in both groups.

Clinical Laboratory Evaluations

Summary

Clinical laboratory data were evaluated in 9 clinical studies (6 controlled, 3 uncontrolled) for patients diagnosed with _____, community acquired pneumonia (CAP) or acute bacterial sinusitis (ABS).

In the controlled clinical studies, the proportion of patients with F2F3-flagged values (laboratory values that changed from baseline by more than a pre-specified amount and were also outside a pre-specified extended normal range) at the end of therapy visit (with the exception of high platelets) in either treatment group was ≤ 0.6% for any specific hematology parameter. The proportion of patients in either treatment group with F2F3-flagged elevated platelets in the controlled studies was 3.7% in the Augmentin XR group and 2.5% in the All Comparators group. In the Augmentin XR group, 73.3% (33/45) of patients with F2F3-flagged elevated platelet values were CAP patients. Given that elevation of platelet count is a recognized response in CAP patients, this low proportion of patients with elevated platelets was not considered to be clinically significant. In the controlled clinical studies, only 10 patients, 5 in each treatment group, reported an adverse experience (AE) of thrombocythemia on-therapy or within 30 days following therapy; only 4 of these patients, 2 patients in each treatment group, had F2F3-flagged elevated platelet values.

In the controlled studies, the proportion of patients in both treatment groups with F2F3-flagged values for any specific liver function parameter was ≤ 1.7% and for any renal function, serum electrolyte, or other metabolic function parameter was ≤ 0.5%. The proportion of patients in the controlled studies in both treatment groups with an F3 transition from screening to the on-therapy visit was ≤1.6% for any specific urinalysis parameter, with the exception of urine white blood cells (WBCs). The proportion of patients with an F3 transition for WBCs in either treatment group was 3.1% and was not deemed to be clinically significant.

The frequencies of F2F3-flagged high platelet, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) values were slightly higher in patients who received Augmentin XR in the uncontrolled studies (6.3%, 2.2%, and 1.2%, respectively) than in patients who received Augmentin XR in the controlled studies (3.7%, 1.6%, and 0.4%, respectively). In general, the frequency and pattern of F2F3-flagged hematology and clinical chemistry parameters and F3 transitions in urinalysis values at the end of therapy visit for Augmentin XR-treated patients in the controlled studies were similar to the results observed in the uncontrolled studies. Similar results were observed for all patients exposed to Augmentin XR.

In CAP Study 546, the frequency and pattern of all F2F3-flagged parameters at the end of therapy visit in Augmentin XR-treated patients were consistent with results in patients treated with Augmentin 875/125mg.

Conclusions

A total of 4144 patients received at least one dose of Augmentin XR 2000/125mg bid in six controlled studies and three non-comparative trials; 1387 patients received comparators in the six completed double-blind, active-comparator clinical studies. The scheduled duration of treatment with Augmentin XR was 7 or 10 days, according to the study protocol. The mean duration of exposure to Augmentin XR was 8.1 days in the controlled studies and 9.1 days in the uncontrolled studies.

Overall and within each indication, demographic characteristics were similar between Augmentin XR and All Comparator treatment groups. Males and females were represented equally in the Augmentin XR Phase 3 program.

The mean age of all Augmentin XR-treated patients was 47 years; 19.2% were ≥65 years old and 7.9% were ≥75 years old. The majority of patients were white and approximately half were enrolled in centers located in the US.

Based on the data provided, the safety profile of Augmentin XR can be summarized as follows:

- Augmentin XR demonstrated an acceptable safety profile in the controlled and uncontrolled clinical studies. The adverse event profile of Augmentin XR in all exposed patients was generally similar across controlled and uncontrolled clinical studies.

- There were no clinically significant issues identified in the new safety data from Studies 547, 557 and 592 when compared to the safety data from the original NDA. The overall adverse event profiles of Augmentin XR were similar in the NDA, new and combined datasets among all exposed, controlled study and uncontrolled study patients. The similar safety profile for the new data compared to the safety profile in the original NDA provides reassurance that the types and frequencies of adverse events are understood for Augmentin XR.

- The adverse event profile of Augmentin XR was similar to that of Augmentin 875/125mg b.i.d. in a direct comparison of the two treatments in Study 546, including gastrointestinal AEs, the body system with the most frequently reported AEs in either treatment group.

- The adverse event profile for Augmentin XR did not differ markedly from the established AE profile for Augmentin 875/125mg b.i.d. as noted in the prescribing information.

- Diarrhea (17.4%) was the only adverse event reported by ≥5% of Augmentin XR-treated patients (all exposed) overall in the Phase 3 clinical studies. Diarrhea was also the most frequently reported AE for patients in the controlled studies (Augmentin XR: 19.8%, All Comparators 9.9%). Overall, diarrhea required corrective treatment for 4.0% of Augmentin XR-treated patients (all exposed). In controlled studies, 4.9% of Augmentin XR and 2.4% of All Comparator-treated patients required corrective therapy for diarrhea. Diarrhea necessitated premature study withdrawal in 0.8% of all exposed Augmentin XR patients. In Study 546 (head to head comparison of Augmentin XR to Augmentin 875/125mg b.i.d.), diarrhea was reported in 18.0% of patients in the Augmentin XR group and in 14.3% of patients in the Augmentin 875/125mg group; the difference between the treatment groups was not statistically significant (P=0.28; 95% CI= -2.6%, 10.1%).

- Patient deaths occurred infrequently in the Augmentin XR Phase 3 studies. All patient deaths that occurred within 30 days of the cessation of therapy were in the CAP program. Most patients who died were over age 65 and had comorbid conditions.

- All serious adverse experiences associated with death were considered by the investigators to be either unrelated or unlikely to be related to Augmentin XR or comparators.

- In the Phase 3 clinical program, small proportions of patients in the Augmentin XR and All Comparators groups reported serious adverse experiences on-therapy or within 30 days post-therapy; of these, small numbers of SAEs in both groups were of suspected or probable relationship to the study medication. The most frequently reported SAE was pneumonia in both treatment groups.

- Serious adverse experiences of diarrhea were reported infrequently (<0.1%); the two SAEs of diarrhea were reported as being related to Augmentin XR.

- The serious adverse event profile of Augmentin XR was comparable to that of Augmentin 875/125mg.

- Small proportions of patients in the Augmentin XR and All Comparators groups experienced AEs or SAEs on-therapy or within 30 days post-therapy that led to withdrawal. The most frequently reported AEs leading to withdrawal were diarrhea and pneumonia in both treatment groups.

- The profile of AEs leading to withdrawal for Augmentin XR was comparable to that observed for Augmentin 875/125mg b.i.d.

- No remarkable or consistent changes in hematology, clinical chemistry (including liver function) or urinalysis parameters were identified in patients who received Augmentin XR in controlled or uncontrolled clinical studies.

- Laboratory profiles for Augmentin XR-treated CAP patients did not differ markedly from profiles for patients who received Augmentin 875/125mg b.i.d.

- In the Augmentin XR group, 73.3% of patients with F2F3-flagged elevated platelet values were CAP patients. Given that elevation of platelet count is a recognized response in CAP patients, this proportion of patients with elevated platelets was not considered to be clinically significant.

- No crystals other than those routinely found in the urine were observed at the on-therapy visit in patients treated with Augmentin XR.

- There were no appreciable differences in the AE profiles reported by gender, age, racial origin or country in the Phase 3 clinical studies. However, the overall proportion of patients reporting AEs was higher in the US compared with the combined non-US centers.

- As with the all exposed patients who received Augmentin XR in the Phase 3 studies, diarrhea was the most frequently reported AE within each demographic subgroup examined. The reporting rate for individual AEs, most notably diarrhea, varied considerably by country.

- The adverse event profiles of Augmentin XR-treated patients were generally similar for patients with —— CAP and ABS.

- The laboratory profiles (hematology, clinical chemistry and urinalysis) of Augmentin XR-treated patients were generally similar for patients with —— CAP and ABS, with the exception of elevated platelets in the CAP studies which occurred in both the Augmentin XR and All Comparators groups.

- The AE and laboratory profiles of Augmentin XR treated patients in the controlled studies by indication were generally similar to the overall AE and laboratory profiles for Augmentin XR-treated patients in the combined controlled studies.

- The profile of serious adverse experiences, including those leading to withdrawal and those associated with death, for the ongoing CAP studies was similar to the profile of the concluded CAP studies (Study 546, Study 556, 557 and an interim analysis of Study 547) with respect to type of serious AE reported and relationship to treatment.

Similar to other formulations of Augmentin, diarrhea remains the most frequently reported AE in this extended release formulation. The rate of withdrawals due to diarrhea was only 0.8% in all patients treated with Augmentin XR. Serious adverse

experiences of diarrhea were reported by only 0.1% (2 patients) of Augmentin XR-treated patients, consistent with conventional Augmentin. No investigator reported a confirmed case of pseudomembranous colitis and few patients were given empiric antibiotics for diarrhea while on-therapy. In conclusion, Augmentin XR was generally well tolerated, and had a similar safety profile to conventional Augmentin in patients treated for [redacted] community acquired pneumonia and acute bacterial sinusitis.

Medical Officer's Conclusions:

The Medical Officer's concurs with the Applicant's conclusions.

Medical Officer's Recommendations:

Dr. Charles Cooper did the review of clinical efficacy data. (Please refer to his review) The recommendation for approval of this submission will be based on the overall efficacy and safety, and will be made by the primary reviewer, Dr. Charles Cooper. As far as safety of Augmentin XR is concerned, I did not find any additional adverse events than those that were already mentioned in the labeling of other approved Augmentin formulations. Though there were more deaths in the Augmentin XR arm, all but 5 of those deaths were in the uncontrolled study where no comparator was used. Most of the deaths occurred after therapy with Augmentin XR was stopped, and occurred in patients more than 65 years of age with comorbid conditions. Thus at this point, the medical officer's conclusions are that Augmentin XR is as safe as other Augmentin products already on the market.
The proposed draft labeling will be reviewed separately.

Nasim Moledina, M.D.
Medical Officer, DAIDP

cc: **NDA 50-785**

HFD-520
HFD-520/MO/NMoledina
HFD-520/MO/CCooper
HFD-520/PM/SSamanta
HFD-520/MTL/JAlexander
HFD-520/Pharm/KSeethaler
HFD-520/Micro/JUnowsky
HFD-520/Chem/SPagay
HFD-520/TValappil
nm/8/29/2002;revised10/15/2002.

Concurrence Only:
HFD-520/Div/Dir/JSoreth

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nasim Moledina
10/16/02 09:42:39 AM
MEDICAL OFFICER

Final paper copy signed off 10/16/2002

John Alexander
10/21/02 04:03:17 PM
MEDICAL OFFICER

Dr. Moledina's Safety Review of Resubmission for Augmentin XR

Janice Soreth
10/21/02 05:26:33 PM
MEDICAL OFFICER

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MEDICAL OFFICER REVIEW OF NDA 50-785: AMOXICILLIN/CLAVULANATE 16:1 (AUGMENTIN XR™)

Date Submitted:	20 December 2000
Date Received:	21 December 2000
Date Assigned:	21 December 2000
Date Action Taken:	20 December 2001

Applicant: GlaxoSmithKline
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101-7929
(215)751-3868

Contact Person: Cynthia D'Ambrosio, Ph.D.
(215)751-3468

Drug: Proprietary Name: Augmentin XR™
Generic Name: Amoxicillin/Clavulanate 16:1

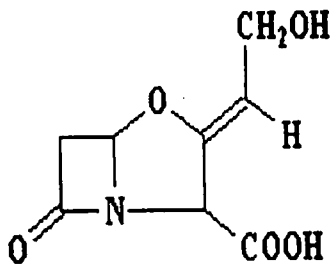
Chemical Name: (amoxicillin)
4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(2R)-amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, [monosodium salt, (2S, 5R, 6R).

(clavulanate)
clavulanate potassium is potassium (*Z*)-(2 *R* , 5 *R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate

Molecular Structure:

Clavulanic Acid

$C_8H_9NO_5$



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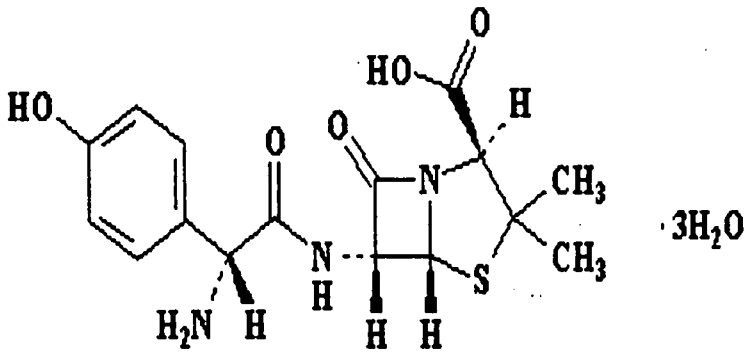
Amoxicillin

$C_{16}H_{19}N_3O_5S \cdot 3H_2O$



Drug Class: Amoxicillin - semi-synthetic penicillin
Clavulanate potassium – naturally occurring beta-lactamase inhibitor isolated from Streptomyces clavuligerus and contains a beta-lactam ring

Formulation: Tablet containing 1000 mg of amoxicillin and 62.5 mg of clavulanate

Route of administration: Oral

Related IND: IND ——

Related NDA's: 50-564, 50-575, 50-597, 50-720, 50-725, 50-726, 50-755, ——

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EXECUTIVE SUMMARY

Introduction

GlaxoSmithKline has submitted NDA 50-785 to the FDA proposing [redacted] indications: community acquired pneumonia (CAP), acute bacterial sinusitis (ABS) with a claim for penicillin-resistant *Streptococcus pneumoniae* (PRSP), [redacted] The product is a new formulation of Augmentin which contains a larger amount of amoxicillin than previous formulations. The new tablets contain amoxicillin and clavulanate in a 16:1 ratio. The proposed dosage is 2,000 mg amoxicillin/125 mg clavulanate (two tablets) orally twice a day. The total daily amount of amoxicillin, 4,000 mg, is 56% more than the current FDA approved Augmentin 875, which provides a total daily dose of amoxicillin of 1,750 mg. The concept which led to the development of this product is that by greatly increasing the total amount of amoxicillin in Augmentin, successful treatment of some strains of PRSP could be achieved. With this aim in mind, pre-clinical pharmacokinetic studies were conducted which revealed that the increased dose of amoxicillin delivered a maximum plasma concentration (Cmax) of approximately 17 µg/mL. The time above a MIC of 4.0 µg/mL was approximately 49% of the dosing interval. Based on this information and discussions with the Division, the sponsor proceeded with clinical development. The goal of this program was to demonstrate clinical efficacy for this product against PRSP with an MIC to penicillin of ≤4.0 µg/ml in the indications of CAP and ABS. The studies conducted for this NDA attempted to accumulate data to support efficacy against PRSP, as well as the safety of this new formulation.

During all developmental meetings with the sponsor, it was the understanding of the Division that the submitted NDA would involve an application for PRSP up to an MIC of 4.0 µg/ml for the indications of CAP and ABS. [redacted]

The NDA submission included data from 5 controlled clinical studies (Study 550, 546, 556, 548, and 549) and two open label studies (Study 547 and 551). The same dose of Augmentin XR (2,000 mg amoxicillin/125 mg clavulanate po B.I.D.) was used in all of the clinical trials.

Shortly after submission of the NDA, the Division requested a re-analysis of safety and efficacy results. This reanalysis excluded patients enrolled from three centers. These centers 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.

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Summary Listing of All Submitted Studies

Study Number	Indication	Study Design	Start-Completion Dates	Number of Subjects	Age (yrs)	Comparator
546	CAP	Randomized, double-blinded, multi-center, Phase III	Nov/99-May/00	516	16-91	Augmentin 875/125 PO B.I.D. x 7 days
547	CAP	Open-label, Non-Controlled, Phase III	Nov/99-May/01	421	16-93	NONE
556	CAP	Randomized, double-blinded, multi-center, Phase III	Nov/99-June/00	347	18-92	Augmentin 1,000/125 PO TID x 10 days
548	—	Randomized, double-blinded, multi-center, Phase III	Nov/99-Mar/00	634	38-91	Clarithromycin 500mg po B.I.D. x 7 days
549	—	Randomized, double-blinded, multi-center, Phase III	Nov/99-Feb/00	673	39-92	Levofloxacin 500mg PO B.I.D. x 7 days
550	ABS	Randomized, double-blinded, multi-center, Phase III	Nov/1999-Feb/00	432	18-75	Levofloxacin 500mg PO B.I.D. x 10 days
551	ABS	Open-label, Non-Controlled, Phase III	Nov/99-June/00	861	16-83	NONE

The applicant presented analyses of clinical cure that included an intent to treat group and a per-protocol Group. A microbiologically evaluable subgroup, comprised of patients with positive baseline sputum cultures was analyzed. This group consisted of cases where the organism isolated at baseline was typical for the indication under study. In addition, two studies (547, 551) which were conducted as open label studies had primary endpoints of microbiologic eradication of baseline typical pathogens. The sponsor chose the per-protocol group as their primary analysis, while the FDA considered both the per-protocol and intent to treat analyses.

Clinical Outcome Summary

FDA review of the applicant's clinical trials for CAP, — ABS was in general agreement with assignments and outcome evaluation. In addition, the applicant's analyses were verified by the FDA review. Exclusion of the 235 patients from studies 548, 549, 550, and 551 did not significantly affect the results of the submission. Clinical outcome rates are listed below for each of the subgroups by study.

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APPLICANT'S CLINICAL EFFICACY RESULTS BY SUBGROUP			
Analysis Population	**Augmentin XR**	**Comparator**	**Treatment Difference, 95% Confidence Interval**
Study 546 (CAP)			
		Augmentin 875*	
Intent to Treat (N=514)	78.0% (199/255)	82.6% (214/259)	-4.6 (-11.4, 2.3)
Per Protocol (N=408)	86.3% (176/204)	91.2% (186/204)	-4.9 (-11.0, 1.2)
Study 556 (CAP)			
		Augmentin 1gr†	
Intent to Treat (N=344)	81.1% (137/169)	85.7% (150/175)	-4.6 (-12.5, 3.2)
Per Protocol (N=232)	91.5% (108/118)	93.0% (106/114)	-1.5 (-8.3, 5.4)
Study 547 (CAP)			
Intent to Treat	82.6% (347/420)	----------	(78.6, 86.1)
Per Protocol	89.2% (297/333)	----------	(85.2, 92.2)
Study 548			
		Clarithromycin	
Intent to Treat (N=585)	79.0% (229/290)	81.4% (240/295)	-2.4 (-8.9, 4.1)
Per Protocol (N=461)	84.6% (187/221)	85.8% (206/240)	-1.2 (-7.7, 5.3)
Study 549			
		Levofloxacin	
Intent to Treat (N=625)	79.8% (245/307)	80.6% (254/318)	-0.8 (-7.1, 5.4)
Per Protocol (N=519)	85.9% (219/255)	87.1% (230/264)	-1.2 (-7.1, 4.6)
Study 550‡ (ABS)			
		Levofloxacin	
Intent to Treat (N=360)	76.4% (136/178)	83.0% (151/182)	-6.6 (-14.9, 1.7)
Per Protocol (N=269)	83.7% (103/123)	84.3% (118/146)	-0.5 (-9.4, 8.3)
Study 551 (ABS)			
Intent to Treat	87.9% (707/804)	----------	(85.4, 90.1)
Per Protocol	92.7% (649/700)	----------	(90.5, 94.5)

* Currently FDA approved Augmentin 875 contains total daily dose of 1,750 mg amoxicillin/250 mg clavulanate

† Non-FDA approved European formulation Augmentin 1gr contains total daily dose of 3,000 mg amoxicillin/375 mg clavulanate

‡ results from Study 550 represent primary endpoint of this study which was combined clinical/radiological response.

The clinical cure rates for Augmentin XR in the Per Protocol population ranged from 83.7%-92.7% for ABS, 84.6%-85.9% for — and from 86.3%-91.5% for CAP. In general, the cure rates tended to be higher for the comparators than for the study drug; however, the prospectively set lower limit of the confidence interval

was not exceeded except for in one study (546). In this study, a sensitivity analysis revealed that failure to meet the goal delta was due to unusual results from certain non-U.S. centers.

Special population analyses did not reveal differences in outcome rates according to gender or race. However, clinical success rates in CAP studies in patients aged ≥65 years in each treatment group were slightly lower than the rates observed in those patients aged <65 years (see integrated summary of efficacy).

Microbiology

Baseline sputum cultures were obtained in all CAP and — trials. Sinus punctures were performed only in study 551, the uncontrolled ABS study.

Microbiological evaluation was based, primarily, on clinical response in patients who had a positive baseline culture. The following tables contain the bacteriolgoical outcomes for studies that included baseline cultures.

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)

Number (%) of Patients with Bacteriological Outcome of Eradicated or Presumed Eradicated by Pre-Therapy Pathogen: ABS Principal Uncontrolled Study 551 (Bacteriology ITT and PP Populations)

	Augmentin XR 2000/125 mg b.i.d.			
	Bacteriology ITT N=359		Bacteriology PP** N=321	
Test of Cure	*n/N**	%	*n/N**	%
All Pathogens	374/426	(87.8)	354/378	(93.7)
S. pneumoniae	102/110	(92.7)	99/101	(98.0)
H. influenzae	75/87	(86.2)	70/78	(89.7)
M. catarrhalis	34/37	(91.9)	32/32	(100.0)
K. pneumoniae	26/27	(96.3)	24/24	(100.0)
H. parainfluenzae	11/14	(78.6)	9/9	(100.0)
MSSA	15/17	(88.2)	15/17	(88.2)

Penicillin Resistant *Streptococcus pneumoniae*

The only FDA approved antibiotic for the treatment of PRSP in adults is Levaquin. Levaquin is currently approved for the treatment of CAP due to PRSP. In the per protocol analysis of that NDA, there were a total of 15 patients from whom PRSP was isolated. All fifteen were successes and 6 of these patients were also found to be bacteremic at enrollment which further bolstered the quality of the evidence.

In this Augmentin XR NDA submission, there were a total of 5 CAP patients, 3 — patients, and 10 ABS patients who had PRSP as the etiology of their infection.

Summary of Penicllin Resistant Pneumococcus in All Indications for NDA 50785

Indication	Number of PRSP isolates (MIC≥2.0mcg/ml)	Per Protocol Success Rate (%)	Intent to Treat Success Rate (%)	Bacteremic
CAP	5	3/4 (75%)	4/5 (80%)	0/5
ABS	10	9/9 (100)	10/10 (100)	0/10
—	3	3/3 (100)	3/3 (100)	0/3

Safety Issues

Overall, there were no serious safety signals present in the safety database of this NDA. There was a higher rate of diarrhea and vaginal moniliasis in the Augmentin XR arm (20.0% and 2.6%) than in the comparator arms (9.3% and 1.2%) for all controlled clinical trials. There was also a higher rate of corrective therapy for diarrhea and vaginal moniliasis in the Augmentin XR arm (5.9% vs. 2.6% in the comparator arm). However, these were not serious nor did they affect compliance or lead to a higher rate of withdrawal.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY/RECOMMENDATION:

Augmentin XR was developed specifically for the treatment of PRSP in patients with CAP and ABS. .. Therefore, the sponsor has requested an indication for CAP and and ABS with a PRSP claim. There are no data in this NDA which indicate that this product offers any additional benefit for the treatment of CAP or than the already approved formulation, Augmentin 875. Augmentin XR contains much more amoxicillin than Augmentin 875, offers no additional benefit, and causes an increase in certain non-serious adverse event which often require corrective therapy. With regards to acute bacterial sinusitis, it is the policy of the Division not to award an indication for ABS due to PRSP until substantial evidence has been provided to support efficacy and safety in patients with community-acquired pneumonia due to PRSP. In addition, it is not clear that 10 isolates of PRSP in ABS as described in this submission, are adequate for the granting of a PRSP claim. Therefore, it can be concluded that this product also offers no additional benefit for the treatment of ABS, and causes an increase in certain non-serious adverse events which often require corrective therapy.

The sponsor has demonstrated efficacy for CAP, ABS, and However, the sponsor has not demonstrated efficacy for PRSP in CAP or PRSP in ABS. Therefore, this formulation offers no added benefits over existing formulations, yet does pose additional risk to patients from side effects, including some that require interventions. On this basis, non-approval is recommended. To pursue further development of Augmentin XR, the sponsor is asked to provide additional evidence of efficacy in the treatment of patients with pneumonia and sinusitis due to *Streptococcus pneumoniae* with reduced susceptibility to penicillin.

APPEARS THIS WAY
ON ORIGINAL

INTEGRATED SUMMARY OF EFFICACY

INTRODUCTION/RATIONALE FOR DEVELOPMENT OF AUGMENTIN XR

Augmentin XR is a sustained release formulation (2000/125mg, 16:1 amoxicillin/clavulanate) intended for b.i.d. treatment of respiratory tract infections. Compared with existing Augmentin formulations, the bilayer tablet of Augmentin XR provides both an increase in amoxicillin to give the new 16:1 ratio and sustained release to maximize the time above the minimum inhibitory concentration (T>MIC), the pharmacokinetic/ pharmacodynamic parameter that correlates best with antibacterial efficacy for beta-lactam antibiotics. Augmentin XR was developed for the treatment of adults with acute bacterial sinusitis (ABS), community-acquired pneumonia (CAP) [redacted], where the involvement of penicillin-resistant Streptococcus pneumoniae (PRSP) is suspected.

Community acquired respiratory tract infections, specifically acute bacterial sinusitis, community acquired pneumonia [redacted], are among the most frequent reasons for antibiotic administration worldwide. Bacterial species, particularly *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are important causes of these infections.

The changing susceptibility pattern of several of the important respiratory pathogens to antibacterial agents, particularly *S. pneumoniae*, has raised concerns about the efficacy of currently available therapies. Of particular concern are the increasing rates of resistance to beta-lactams as mediated not only by the production of beta-lactamases but also by changes in penicillin binding proteins. This has resulted in an increasing prevalence of penicillin-resistant *S. pneumoniae* (penicillin MIC ≥2 μg/mL according to NCCLS 2000 guidelines) and beta-lactamase producing *H. influenzae*.

In order to provide efficacy against *S. pneumoniae* strains with elevated MICs, the sponsor developed Augmentin XR to increase the T>MIC over current Augmentin formulations. By prolonging the time for which serum concentrations of amoxicillin remain above the MIC (T>MIC), the new sustained release formulation will provide an effective treatment for infections involving *S. pneumoniae* with elevated penicillin and amoxicillin MICs. Additionally, the clavulanate component enables the amoxicillin in Augmentin XR to maintain activity against beta-lactamase-producing organisms such as *H. influenzae* and *M. catarrhalis*.

Rationale for Dose Selection

The Augmentin XR bilayer tablet is composed of an immediate release layer [redacted], and a sustained release layer [redacted] Each tablet therefore contains the equivalent of 1000mg of amoxicillin and 62.5mg of clavulanic acid. The dose regimen of this new formulation investigated in the clinical program, is two bilayer tablets, ie. 2000mg of amoxicillin and 125mg of clavulanic acid, taken twice daily, every 12 hours.

The immediate release layer of the bilayer tablet is designed to provide the desired maximum amoxicillin plasma concentration (Cmax), and the sustained release layer is designed to provide the desired time above the minimum inhibitory concentration (T>MIC). The amoxicillin dose of 2000mg (1000mg per tablet), [redacted], provides a mean Cmax of approximately 17 μg/mL and a mean T>MIC of approximately 49% of the 12 hour dosing interval for strains with an MIC of 4 μg/mL.

While the proposed daily dose of amoxicillin of 4g is an increase over the usual 7:1 (875/125 mg) or 8:1 b.i.d. regimens, this dose is within the range of approved doses for amoxicillin in certain countries (ie, Nordic and Baltic countries). The dose of clavulanic acid, 125mg, remains the same as in currently marketed formulations of Augmentin and the pharmacokinetics of clavulanate compared to the 7:1 formulation are unaltered. The twice daily regimen of 125mg of clavulanic acid has been shown to have good efficacy against common beta-lactamase producing bacteria with a more acceptable gastrointestinal adverse event profile compared with 125mg three times daily.

MO COMMENT: This formulation is not a true sustained release formulation. Also, the time release characteristics of this formulation are not related to the [redacted] contained in the formulation.

Overview of Clinical Program

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

Acute Bacterial Sinusitis (ABS)

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

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

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

Community Acquired Pneumonia (CAP)

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

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

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

———

Principal Controlled Studies in —
Study 548 - A randomized, double-blind, double-dummy, multicenter, parallel group study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days versus oral clarithromycin 500mg twice daily for 7 days in the treatment of —

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

Financial Disclosure Information

There were four investigators who participated in clinical research for GSK as part of this NDA who had a financial interst in GSK. Investigators [redacted] all had stock holdings of [redacted] These investigators enrolled relatively small numbers of patients. [redacted] (both at Center [redacted] enrolled 10 patients in study [redacted] Both at Center [redacted] enrolled 9 patients in study [redacted] (at Center [redacted] enrolled 8 patients into study [redacted] He enrolled 6 patients at Center [redacted] in study [redacted]

Overall, 56 investigators out of a total of 2,398, did not complete financial disclosure forms despite diligent efforts by the sponsor.

EFFICACY OF AUGMENTIN XR IN ACUTE BACTERIAL SINUSITIS

Acute Bacterial Sinusutis (Studies 550 and 551)

One principal controlled clinical study and one principal uncontrolled study were submitted by the sponsor to demonstrate the efficacy of Augmentin XR in the treatment of ABS.

Clinical Studies of Augmentin XR in ABS

Study	Treatment Regimen	Duration	N*	Geographic Region
Principal Controlled Study				
550	Augmentin XR 2000/125mg b.i.d.	10 days	214	Europe and US
	Levofloxacin 500mg qd	10 days	218	
Principal Uncontrolled study				
551	Augmentin XR 2000/125mg b.i.d.	10 days	861	US and Europe

* N= number of patients randomized to treatment (N=enrolled for non-comparative study)

MO COMMENT: The design of both studies was consistent with current FDA draft guidances for the study of acute bacterial sinusitis. Study 550 was a comparative clinical study in which no antral punctures were performed. Study 551 was a open lable, non-comparative bacteriolgoical study in which all patients received antral puncture.

Summary of Study Design, Procedures, and Endpoints, Studies 550, 551

Principal Study 550 was a randomized, multicenter, double-blind, double-dummy, parallel group study designed to evaluate the clinical and bacteriological efficacy and safety of Augmentin XR 2000/125mg b.i.d. for 10 days in comparison with levofloxacin 500mg qd for 10 days. Levofloxacin was chosen as the active comparator for this study, since it is indicated for the treatment of ABS, and has been used frequently for this condition in the US and other countries worldwide. Clinical effectiveness of levofloxacin in the treatment of ABS has been established and levofloxacin has similar *in vitro* activity against pneumococci susceptibile to penicillin and resistant to penicillin. Levofloxacin does not have an indication for [redacted]

Principal Study 551 was a non-comparative trial designed to assess the bacteriological and clinical efficacy and safety of oral AugmentinXR for 10 days in the treatment of patients with ABS, particularly those with penicillin-resistant *S. pneumoniae* (PRSP).

The study population for both studies was selected in accordance with the current draft guidance for the investigation of agents to treat ABS and was considered to be representative of patients with well-defined ABS, without serious complications. Patients were male or female, aged ≥18 years, with a clinical diagnosis

of ABS. For both studies, the signs and symptoms of ABS were to be of at least 7 days but less than 28 days duration, and included purulent nasal discharge or purulence in the nasal cavity on examination and at least one *major* or two *minor* criteria as follows:

> *Major* criteria: facial pain/pressure/tightness over affected sinus(es), facial congestion/fullness or nasal obstruction/blockage.
>
> *Minor* criteria: tooth pain, earache, non-vascular headache, sore throat, cough, halitosis, fever (as defined in the Study 550 Clinical Report), change in perception of smell or periorbital swelling.

Furthermore, the episode of ABS was to be radiologically confirmed (i.e., either via a Water's view X-ray or CT scan) within the 72 hour period prior to randomization.

Patients were not permitted to enter the study if they had conditions which included cystic fibrosis, tooth abscess, proximal nasal polyp disease, a history of chronic sinusitis, sepsis, intraorbital or intracranial complications that would have interfered with the interpretation of radiological images of the affected sinus(es), or prior endoscopic sinus surgery which invaded nasal cavities, or any other complicating infection or disease that would compromise evaluation of the study. Patients who required hospitalization, parenteral antibacterial therapy, or had signs and symptoms of a disseminated infection were also excluded, as were patients who had received any other systemic antibacterial agent within 7 days of study entry. 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. The only difference between the two studies was that Study 551 had a lower age limit (≥16 years) and signs and symptoms of ABS could be of 3 days duration for severe cases.

For both studies, after randomization into the study, patients were scheduled to attend the clinic during therapy (Day 3-5), at end of therapy (Day 12-14), and at test of cure (Day 17-24). For the purpose of the analysis, the evaluable visit windows were extended to Day -2 to 1 for screening, Day 11-16 for end of therapy and Day 17-28 for test of cure.

In both studies, evaluation of the clinical signs and symptoms of ABS was conducted at the study assessments. A repeat sinus X-ray (Water's view) or CT scan (whichever was performed at the Screening visit) was performed at the test of cure visit, but also at other visits for patients requiring further antibacterial treatment, ie clinical failures. Sinus endoscopy or rhinoscopy (performed at selected centers only) was generally only performed at the screening visit. However, at some study sites, this was repeated in the case of clinical failure. For Study 551, specimens for bacteriological evaluation were collected by sinus puncture from all patients at screening. The procedure was to be repeated in the case of clinical failures at any time during the study.

Efficacy Variables

Primary Efficacy Evaluation for Study 550

Combined clinical and radiological ***response*** (success, failure or unable to determine) at test of cure (Visit 4) was the primary efficacy variable. Based on the clinical and the radiological outcome, a patient's combined clinical and radiological ***response*** at test of cure was defined as follows, carrying forward radiological outcomes of 'worse' or 'unable to determine' at end of therapy to test of cure for withdrawals and taking not done cases as 'unable to determine':

> *Success*: The patient's clinical outcome at test of cure was 'success' and the radiological outcome was 'improved' or 'unchanged'.
>
> *Failure*: The patient's clinical outcome at end of therapy was 'failure' or the clinical outcome at test of cure was 'recurrence', and/or the patient's radiological outcome at test of cure was 'worse'.

Unable To Determine: Either (i) the patient's clinical outcome at end of therapy or test of cure was 'unable to determine' and the radiological outcome at test of cure was 'improved', 'unchanged', 'unable to determine' or 'unknown', or (ii) the clinical response at test of cure was 'success' and the radiological outcome was 'unable to determine' or 'unknown'.

Patients whose clinical outcome was 'unable to determine' were excluded from the Clinical PP population. However, a radiological outcome of 'unable to determine' in conjunction with a clinical outcome of 'success' resulted in a combined response of 'unable to determine'. Since patients with a radiological outcome of 'unable to determine' were not excluded from the Clinical PP population, 'unable to determine' was a valid category for combined clinical and radiological response in the Clinical PP population.

Patients whose clinical response was failure at end of therapy, but who subsequently became protocol violators at the test of cure visit were included as failures in the Clinical PP test of cure population because they satisfied the criteria for being included in the test of cure failure group prior to violating the protocol.

MO COMMENT: These criteria used for determination of clinical response are adequate.

For patients who were clinical successes at end of therapy, the clinical outcome at test of cure (i.e., clinical success, clinical recurrence or unable to determine) was assigned by the investigator based on the changes in signs and symptoms of ABS from the screening assessment. Radiological outcome was determined by an independent assessor (e.g., radiologist) based on the evaluation of Water's view X-rays or coronal CT scans taken at screening and test of cure (or at time of withdrawal). Radiological outcome was assessed as improved (including resolution), unchanged, worse or unable to determine. A patient's combined clinical and radiological response at test of cure was then determined as follows:

Determination of Combined Clinical and Radiological Response at Test of Cure, Study 551

Clinical Outcome	Radiological Outcome	Combined Response
- Test of cure clinical success	AND: improved or unchanged	⇒ *Success*
- Clinical recurrence at test of cure - Clinical failure at end of therapy	AND/OR: worse	⇒ *Failure*
- Unable to determine at test of cure - Unable to determine at end of therapy	AND: improved, unchanged, unable to determine or unknown	⇒ *Unable to Determine*
- Test of cure clinical success	AND: unable to determine or unknown	⇒ *Unable to Determine*

Patients with a clinical outcome of clinical failure or unable to determine at end of therapy were carried forward to test of cure. For withdrawals, radiological outcomes of 'worse' or 'unable to determine' at end of therapy were carried forward to test of cure.

The key secondary efficacy variables were clinical response at test of cure and end of therapy. A patient's clinical response (clinical success or clinical failure) was determined from the clinical outcome assigned at test of cure (as described above) and end of therapy.

The focus of Study 550 was on clinical rather than bacteriological endpoints, and only a subset of patients were subject to bacteriological investigations.

Primary Efficacy Evaluation for Study 551

For Study 551, the primary efficacy variable was the per patient bacteriological response (success or failure) at test of cure for the Bacteriology ITT population. The bacteriological evaluation was based on the assessment of pathogens isolated from sinus puncture samples collected from all patients at screening and at the time of any clinical failure. For patients with a pre-therapy pathogen but without a repeat sinus puncture culture at 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 sample. 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 time points.

The protocol for Study 551 identified the Bacteriology ITT population as the population for the principal analysis. The Bacteriology ITT population contained all enrolled patients who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening. The principal analysis was repeated for the Bacteriology PP population in which patients with a bacteriological outcome of Unable to Determine were excluded.

Data Sets for Analysis

For Study 550, the analysis of the clinical efficacy variables included two patient populations which were defined 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.

For both studies, patients were excluded from the Clinical PP population only from the time that the protocol violation occurred.

The protocol for Study 550 identified the PP population as the population for the principal analysis, with the ITT population providing confirmatory analysis. Patients with a clinical outcome of Unable to Determine were excluded from the Clinical PP population. However, in the ITT analyses, clinical outcomes of Unable to Determine were classified as clinical responses of failure, representing a worst case approach.

MO COMMENT: Only those protocol violations which were thought to effect efficacy were excluded from the efficacy analysis. Such protocol violations were determined prior to breaking the blind and are discussed in detail in the NDA (section 3.13.5). They have been reviewed by the MO and are reasonable.

Study 550 was designed to demonstrate that Augmentin XR was at least as good as the active comparator. The planned sample size of 400 patients (to provide 300 clinically evaluable patients) was calculated based on an underlying equivalent clinical response rate of 80% at test of cure. The estimation of sample size used 90% power to show that the lower bound of the two-sided 95% confidence interval (CI) for the difference in response rate (Augmentin XR minus levofloxacin) was no less than the pre-defined non-inferiority limit of –15%.

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-inferiority of Augmentin XR was concluded if the lower limit of the CI was greater than or equal to the non-inferiority limit.

The populations defined for analysis for Study 551 were as follows:

- **Bacteriology ITT:** all enrolled patients who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening.
- **Bacteriology PP**: a subset of the Bacteriology ITT population (i.e., all patients had at least one pre-therapy pathogen identified at screening) which excluded patients who violated the protocol to an extent that could affect treatment efficacy.
- **Intent-to-treat (ITT):** all enrolled 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.

Patients were excluded from the PP populations only from the time that the protocol violation occurred. Hence, the Clinical PP and Bacteriology PP populations may have contained different numbers of patients at end of therapy and test of cure.

For Study 551, the planned sample size was based on previous experience from a study of similar design that showed only 17% of recruited patients had an evaluable S. pneumoniae isolate, of which approximately 9% of the S. pneumoniae isolates were penicillin-resistant. Therefore, in order to obtain an adequate sample, it was anticipated that approximately 600 patients would be required. Recruitment was extended to more than 800 patients to ensure that at least 10 patients with PRSP were entered into the study.

Demographic Characteristics

There were no marked demographic differences between the various populations within each study. The table below summarized key demographic characteristics from both studies 550 and 551.

Demographic Characteristics: ABS Studies 550 and 551										
	STUDY 550								**STUDY 551**	
	Clinical PP				**ITT**				**ITT**	**Bacteriol ITT**
	Augmentin XR		**Levofloxacin**		**Augmentin XR**		**Levofloxacin**		**Augmentin XR 2000/125mg b.i.d.**	
Demographic/ Baseline Characteristic	**2000/125mg b.i.d. N=123**		**500mg qd N=140**		**2000/125mg b.i.d. N=178**		**500mg qd N=182**		**N=804**	**N=359**
Gender, n (%)										
Male	46	(37.4)	58	(41.4)	69	(38.8)	76	(41.8)	347 (43.2)	159 (44.3)
Female	77	(62.6)	82	(58.6)	109	(61.2)	106	(58.2)	457 (56.8)	200 (55.7)
Age (yrs)										
Mean (SD)	42 (13.7)		40.2 (13.2)		41 (13.6)		40.1 (13.4)		40.8 (13.7)	40.7 (14)
Range	18-75		18-73		18-75		18-73		16-83	16-83
Race, n (%)										
White	117	(95.1)	120	(85.7)	166	(93.3)	157	(86.3)	720 (89.6)	327 (91.1)
Black	2	(1.6)	12	(8.6)	5	(2.8)	16	(8.8)	41 (5.1)	15 (4.2)
Oriental	1	(0.8)	2	(1.4)	2	(1.1)	3	(1.6)	3 (0.4)	1 (0.3)
Other*	3	(2.4)	5	(3.6)	5	(2.8)	5	(2.7)	40 (5.0)	16 (4.5)
Unknown	0	-	1	(0.7)	0	-	1	(0.5)	-	-

Disposition

Study 550
In the principal ABS Study 550, a total of 363 patients were randomized on a 1:1 basis to receive treatment with either Augmentin XR or levofloxacin (Augmentin XR: 179 patients, levofloxacin: 184 patients). There were 360 patients in the ITT population since 3 patients were withdrawn before treatment was given; two of these patients withdrew their consent and the sinus X-ray was normal in the case of the third patient.

A total of 20 patients (5.5%) withdrew from Study 550 (Augmentin XR: 15/179, 8.4%, levofloxacin: 5/184, 2.7%). There were no statistically significant differences between treatment groups with respect to the total numbers of patients withdrawn or the numbers withdrawn due to an adverse experience. The most frequent reason for withdrawal was patients being lost to follow up. No patients withdrew due to insufficient therapeutic effect.

The disposition of patients in the principal ABS Study 550, including reasons for withdrawal, are tabulated by treatment group in the table below.

Patient Disposition: ABS Principal Controlled Study 550

Population	Augmentin XR 2000/125mg b.i.d.		Levofloxacin 500mg qd	
Randomized	179		184	
Received Study Medication (ITT)	178		182	
Completed Study	163		177	
Reasons for Withdrawal (ITT), n (%):				
Adverse Experience	5	(2.8)	1	(0.5)
Protocol Deviation*	5	(2.8)	3	(1.6)
Lost to Follow-up	5	(2.8)	1	(0.5)
Total Withdrawn, n (%)	15	(8.4)	5	(2.7)
Clinical PP at End of Therapy	129		145	
Clinical PP at Test of Cure	123		140	

* including non-compliance
Note: In addition to the withdrawals tabulated above, patient 550.022.01222 in the Augmentin XR group had an adverse experience which was recorded with action of 'drug stopped'. The investigator, however, reported that the patient had completed the study after 8 days of treatment.

Study 551
A total of 806 patients were enrolled into Study 551. Of these 806 patients, 804 patients received study medication and were therefore included in the ITT population. One patient was enrolled but withdrew from the study before receiving study medication, the other patient was lost to follow up at Visit 1.

The Bacteriology-ITT population comprised the 359 patients in the ITT population (44.7%) who had a least one pathogen identified at screening.

In the ITT population, 803 patients (93.5%) completed the study. For the 50 patients who withdrew (6.2%), the most frequent reason for withdrawal was protocol deviation (24 patients, 2.8%). There were no withdrawals due to insufficient therapeutic effect.

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The disposition of patients in Study 551 are shown in the table below:

Patient Disposition: ABS Principal Uncontrolled Study 551
(All Enrolled Patients)

Population	Augmentin XR 2000/125mg b.i.d.
Enrolled	806
Received Study Medication (ITT)	804
Completed Study	754
Bacteriology ITT	359
Bacteriology PP at End of Therapy	327
Bacteriology PP at Test of Cure	321
Clinical PP at End of Therapy	712
Clinical PP at Test of Cure	700

Bacteriology at Screening for Study 551
In the Bacteriology ITT population, the most prevalent pathogens isolated at screening were *S. pneumoniae, H. influenzae, M. catarrhalis, K. pneumoniae, H. parainfluenzae* and MSSA. The incidence of these key pathogens were similar in the Bacteriology ITT and Bacteriology PP test of cure populations. The majority of patients from whom *S. pneumoniae, H. influenzae, M. catarrhalis* or MSSA were isolated presented with single pathogen infections. Approximately half of the patients from whom *K. pneumoniae* and *H. parainfluenzae* were isolated, were also infected with one or more other pathogens.

The susceptibility (in terms of MIC and % susceptible, intermediate and resistant) of the key pathogens (*S. pneumoniae, H. influenzae, M. catarrhalis, K. pneumoniae, H. parainfluenzae* 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 the Bacteriology ITT population, at least 90% of isolates of the key pathogens that had an MIC performed were susceptible to amoxicillin/clavulanic acid, cefuroxime and levofloxacin based on breakpoints defined by the NCCLS, 2000.

Ten isolates (8.8%) of *S. pneumoniae* were resistant to penicillin (penicillin MIC ≥2 μg/mL). Five isolates had a penicillin MIC of 4 μg/mL, of which three were also resistant to amoxicillin/clavulanic acid with MICs 8 μg/mL. The remaining 5 PRSP isolates had an MIC of 2 μg/mL and one of these isolates had an amoxicillin/clavulanic acid MIC of 8 μg/mL. Eight of the PRSP isolates were also resistant to macrolides. Eighteen isolates of *S. pneumoniae* (16%) were resistant to erythromycin based on the breakpoint defined by NCCLS, 2000 (MIC ≥1μg/mL). Nine of these isolates had an erythromycin MIC ≥ 32 μg/mL.

Seventeen isolates of *H. influenzae* (17.9%), 36 isolates of *M. catarrhalis* (81.8%), 22 isolates of MSSA (88%) and one isolate of *H. parainfluenzae* (3.8%), were beta-lactamase positive. No isolate was beta-lactamase negative/ampicillin resistant.

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The number of patients with key pathogens associated with ABS at the screening visit from Study 551 are tabulated below.

Number (%) of Patients with Key Pathogens Associated with ABS at Screening: ABS Principal Uncontrolled Study 551 (Bacteriology ITT and Bacteriology PP Test of Cure Populations)

Pre-Therapy Pathogen	Augmentin XR 2000/125mg b.i.d.			
	Bacteriology ITT N=359		Bacteriology PP N=321	
	n	(%)	n	(%)
Total *S. pneumoniae*	110	(30.6)	101	(31.5)
Total *H. influenzae*	87	(24.2)	78	(24.3)
Total *M. catarrhalis*	37	(10.3)	32	(10.0)
Total *K. pneumoniae*	27	(7.5)	24	(7.8)
Total *H. parainfluenzae*	14	(3.9)	9	(2.8)
Total MSSA*	17	(4.7)	17	(5.3)

Note: Some patients may have more than one pathogen.
* Only patients with methicillin-susceptible *S. aureus* (MSSA) isolates are included in this table. One patient in the Bacteriology ITT population had a methicillin-resistant *S. aureus* (MRSA) isolate.

Efficacy Results

Primary Efficacy Endpoint/Study 550
The primary efficacy variable in the principal controlled ABS study (Study 550) was the combined clinical and radiological response at test of cure. The proportion of patients with a combined clinical and radiological response of success, failure or unable to determine, together with the treatment differences and 95% CIs for the Clinical PP and ITT populations are presented in the table below.

Combined Clinical and Radiological Response at Test of Cure: ABS Principal Controlled Study 550 (Clinical PP and ITT Populations)

	Augmentin XR 2000/125mg b.i.d.		Levofloxacin 500mg qd	
Clinical PP	N=123		N=140	
Success, n (%)	103	(83.7)	118	(84.3)
Failure, n (%)	18	(14.6)	20	(14.3)
Unable to Determine, n (%)	2	(1.6)	2	(1.4)
Treatment Difference, %*	-0.5			
95% CI	(-9.4, 8.3)			
ITT	N=178		N=182	
Success, n (%)	136	(76.4)	151	(83.0)
Failure, n (%)	26	(14.6)	24	(13.2)
Unable to Determine, n (%)	16	(9.0)	7	(3.8)
Treatment Difference, %*	-6.6			
95% CI	(-14.9, 1.7)			

In the Clinical PP population at test of cure, the success rate was 83.7% in the Augmentin XR group and 84.3% in the levofloxacin group. The slightly lower success rates in the ITT population, 76.4% in the Augmentin XR group and 83.0% in the levofloxacin group, are accounted for by the patients with a clinical outcome of Unable to Determine' that were included as clinical failures in the ITT population and who were excluded from the Clinical PP population.

MO COMMENT: After review of the protocol, submitted datasets, and CRF sample the sponsor's analysis is accepted as valid. The lower bound of the 95% confidence interval for the ITT analysis was not as good as that for the PP analysis. In fact, it just barely meets the goal delta of –0.15. This is the result of two factors. The

first is the removal of 68 subjects from the study analysis due to questionable data integrity which resulted in a widening of the confidence interval. Second, a larger number of patients in the Augmentin XR group were "unable to determine" for outcome. Review of the submitted data did not reveal a specific reason (i.e., lack of treatment effect, adverse events) why these patients were categorized as "unable to determine."

The percentages of patients who were evaluable for the efficacy analysis are acceptable. Also, a review of the patients who were excluded from the analysis because they received other antibiotics were reviewed by the MO and it was determined that these patients were not treatment failures. The reasons for exclusion from the efficacy analysis appear to be somewhat similar between the two arms, although there were some differences. There were more patients in the study drug arm who had a clinical outcome of "unable to determine" (11 vs. 3). MO review of these patients did not reveal any particular pattern. Of the 11 patients in the study drug arm, 4 were lost to follow up, 2 each missed visit three or withdrew due to an adverse event (diarrhea), and one each missed visit 4, met exclusion criteria, and withdrew due to pregnancy. Of the 3 patients in the control arm, one was categorized as unable to determine because of "lost to follow up" and two did not have a visit 4 evaluation.

Secondary Efficacy Endpoints/Study 550

The key secondary efficacy variables were clinical response at test of cure and end of therapy. Although the study was not designed to demonstrate non-inferiority for secondary variables, the confidence interval for the treatment difference for the secondary efficacy variable is discussed relative to the limit set for non-inferiority (i.e., ≥-15%).

The key secondary efficacy variables are summarized in the table below:

Clinical Response at Test of Cure and End of Therapy: ABS Principal Controlled Study 550 (Clinical PP and ITT Populations)

	Test of Cure		End of Therapy	
	Augmentin XR 2000/125mgb.i.d.	Levofloxacin 500mg qd	Augmentin XR 2000/125mg b.i.d.	Levofloxacin 500mg qd
Clinical PP				
N	123	140	129	145
Success, n (%)	107 (87.0)	124 (88.6)	121 (93.8)	139 (95.9)
Failure, n (%)	16 (13.0)	16 (11.4)	8 (6.2)	6 (4.1)
Treatment Difference, %	-1.6		-2.1	
95% CI	(-9.5, 6.4)		(-7.3, 3.2)	
ITT				
N	178	182	178	182
Success, n (%)	146 (82.0)	161 (88.5)	160 (89.9)	174 (95.6)
Failure, n (%)	32 (18.0)	21 (11.5)	18 (10.1)	8 (4.4)
Clinical Failure at End of Therapy, n (%)	10 (5.6)	7 (3.8)	10 (5.6)	7 (3.8)
Clinical Recurrence, n (%)	11 (6.2)	11 (6.0)	- -	- -
Unable to Determine, n (%)	11 (6.2)	3 (1.6)	8 (4.5)	1 (0.5)
Treatment Difference, %	-6.4		-5.7	
95% CI	(-13.7, 0.9)		(-11.1, 0.4)	

Primary Efficacy Endpoint/ Study 551

The primary efficacy endpoint for the uncontrolled study (Study 551) was the per patient bacteriological response (success or failure) at test of cure for the Bacteriology ITT population. The proportion of patients with a bacteriological response of success or failure, together with 95% CIs for the Bacteriology ITT and Bacteriology PP populations is shown in the following table.

Bacteriological Response at Test of Cure: ABS Principal Uncontrolled Study 551 (Bacteriology ITT and Bacteriology PP Populations)

Augmentin XR 2000/125mg b.i.d.		
Bacteriology ITT	**N=359**	
Success, n (%)	315	(87.7)
Failure, n (%)	44	(12.3)
Known Failure, n (%)	26	(7.2)
Unable to Determine, n (%)	18	(5.0)
95% CI for Success Rate	83.8, 90.9	
Bacteriology PP	**N=321**	
Success, n (%)	299	(93.1)
Failure, n (%)	22	(6.9)
95% CI for Success Rate	89.7, 95.6	

There was a high success rate for bacteriological response at test of cure: 88.0% for the Bacteriology ITT population and 93.5% for the Bacteriology PP population. The results of the observed case analysis of bacteriological response at test of cure were similar, with a success rate in the Bacteriology ITT population of 92.4% (95% CI 89.2, 94.7) and was therefore consistent with the conservative approach of the principal analysis.

Secondary Efficacy Variables/Study 551

There also was a high success rate for the key secondary efficacy variables, bacteriological response at end of therapy and clinical response at test of cure and end of therapy. These results corroborate the findings of the primary efficacy variable. The results of the these secondary efficacy variables are shown in the following tables:

Clinical Response at Test of Cure and End of Therapy: ABS Principal Uncontrolled Study 551 (ITT and Clinical PP Populations)

	Augmentin XR 2000/125mg b.i.d. for 10 days			
Clinical Response	**Test of Cure**		**End of Therapy**	
ITT	**N=804**		**N=804**	
Success, n (%)	707	(87.9)	755	(93.9)
Failure, n (%)	97	(12.1)	49	(6.1)
Clinical Failure at End of Therapy, n (%)	25	(3.1)	25	(3.1)
Clinical Recurrence, n (%)	36	(4.5)	-	-
Unable to Determine, n (%)	36	(4.5)	24	(3.0)
95% CI for Success Rate	85.4, 90.1		92.0, 95.4	
Clinical PP	**N=700**		**N=712**	
Success, n (%)	649	(92.7)	693	(97.3)
Failure, n (%)	51	(7.3)	19	(2.7)
95% CI for Success Rate	90.5, 94.5		95.8, 98.3	

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Bacteriological Response at End of Therapy: ABS Principal Uncontrolled Study 551 (Bacteriology ITT and Bacteriology PP Populations)

	Augmentin XR 2000/125mg b.i.d.	
Bacteriology ITT	**N=359**	
Success, n (%)	336	(93.6)
Failure, n (%)	23	(6.4)
Known Failure, n (%)	12	(3.3)
Unable to Determine, n (%)	11	(3.1)
95% CI for Success Rate	90.4, 95.8	
Bacteriology PP	**N=327**	
Success, n (%)	317	(96.9)
Failure, n (%)	10	(3.1)
95% CI for Success Rate	94.3, 98.4	

Combined Clinical and Radiological Response at Test of Cure: ABS Principal Uncontrolled Study 551 (ITT and Clinical PP Populations)

	Augmentin XR 2000/125mg b.i.d.	
ITT	**N=804**	
Success, n (%)	682	(84.8)
Failure, n (%)	70	(8.7)
Unable to Determine, n (%)	52	(6.5)
95% CI for Success Rate	82.1, 87.2	
Clinical PP	**N=700**	
Success, n (%)	628	(89.7)
Failure, n (%)	59	(8.4)
Unable to Determine, n (%)	13	(1.9)
95% CI for Success Rate	87.2, 91.8	

Results of Eradication of Key Pathogens in ABS Studies

In Study 550, only a very small percentage of patients had pathogens isolated. These pathogens were not isolated via the technique of antral puncture and instead were collected using the technique of rhinoscopy. This technique is still considered investigational for the purposes of conducting clinical trials. For this reason, the microbiological results from Study 550 were not pooled with those from Study 551 and are not reported here.

Pathogens identified at screening in Study 551 which were eradicated or presumed eradicated (overall eradication rate) at test of cure and end of therapy are summarized in the table below for all initial pathogens combined and for the key individual pathogens associated with ABS. Very few patients were willing to undergo repeat sinus puncture and so this procedure was repeated only in the case of clinical failure. As a result, only a small number of pathogens were documented as eradicated (2.1%, 11/521 of initial pathogens). Therefore in the table, pathogens confirmed eradicated and pathogens presumed eradicated (based on clinical success) are combined. It should be noted that 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.

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Number (%) of Patients with Bacteriological Outcome of Eradicated or Presumed Eradicated by Pre-Therapy Pathogen: ABS Principal Uncontrolled Study 551 (Bacteriology ITT and PP Populations)

	Augmentin XR 2000/125 mg b.i.d.			
	Bacteriology ITT		Bacteriology PP**	
Test of Cure	N=359		N=321	
	*n/N**	%	*n/N**	%
All Pathogens	374/426	(87.8)	354/378	(93.7)
S. pneumoniae	102/110	(92.7)	99/101	(98.0)
H. influenzae	75/87	(86.2)	70/78	(89.7)
M. catarrhalis	34/37	(91.9)	32/32	(100.0)
K. pneumoniae	26/27	(96.3)	24/24	(100.0)
H. parainfluenzae	11/14	(78.6)	9/9	(100.0)
MSSA	15/17	(88.2)	15/17	(88.2)
End of Therapy	N=359		N=327	
	*n/N**	%	*n/N**	%
All Pathogens	393/426	(92.3)	374/386	(96.9)
S. pneumoniae	104/110	(94.5)	101/101	(100.0)
H. influenzae	84/87	(96.5)	78/80	(97.5)
M. catarrhalis	35/37	(94.6)	32/32	(100.0)
K. pneumoniae	26/27	(96.3)	24/24	(100.0)
H. parainfluenzae	14/14	(100.0)	11/11	(100.0)
MSSA	16/17	(94.1)	16/17	(94.1)

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

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

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

In the Bacteriology ITT population, 87.8% of the initial pathogens were either eradicated or presumed eradicated at test of cure. Similar results were seen in the Bacteriology PP population with an overall eradication rate of 93.7% at test of cure. The overall eradication rate for *S. pneumoniae* was 92.7% at test of cure in the Bacteriology ITT population and 98.0% in the Bacteriology PP population.

At end of therapy in the Bacteriology ITT population, the majority of the initial pathogens were either eradicated or presumed eradicated (92.3%). Similar results were seen in the Bacteriology PP population with an overall eradication rate of 96.9% at end of therapy. For each key pathogen, a high percentage were eradicated or presumed eradicated at end of therapy in the Bacteriology ITT population. Notably, the eradication rate (eradicated plus presumed eradicated) for *S. pneumoniae* was 94.5% in the Bacteriology ITT population and 100% in the Bacteriology PP population.

Resistant Pathogens

All ten patients in the Bacteriology ITT population (9 in the Bacteriology PP population at test of cure) with PRSP isolates at screening were clinical and bacteriological successes at test of cure (*S. pneumoniae* presumed eradicated in each case). Eight of these isolates were also macrolide-resistant.

Seventeen patients in the Bacteriology ITT population had erythromycin resistant *S. pneumoniae*. Overall, 15 patients (88.2%) were both clinical and bacteriological successes at test of cure (*S. pneumoniae* presumed eradicated in each case). The overall eradication rate for macrolide (erythromycin)-resistant *S. pneumoniae* in the Bacteriology PP population at test of cure was similar (92.9%).

For patients with beta-lactamase positive isolates of *H. influenzae, M. catarrhalis* and MSSA at screening, the majority were eradicated or presumed eradicated at test of cure. Eradication rates ranged from 85.7% (12/14 isolates) for beta-lactamase positive isolates of *H. influenzae* to 90.0% (27/30) for beta-lactamase positive isolates of *M. catarrhalis* in the Bacteriology ITT population. Overall eradication rates for these beta-lactamase producing isolates were similar or slightly higher in the Bacteriology PP population.

A summary of the combined bacteriological eradication and presumed bacteriological eradication rates for PRSP (penicillin MIC ≥2 μg/mL), macrolide-resistant *S. pneumoniae* (erythromycin MIC ≥1 μg/mL), and key beta-lactamase producing strains in Study 551, is presented in the following table.

Number (%) of Patients with Bacteriological Outcome of Eradicated or Presumed Eradicated by Selected Resistant Pathogen and Beta-Lactamase Production at Test of Cure: ABS Principal Uncontrolled Study 551 (Bacteriology ITT and PP Populations)

	Augmentin XR 2000/125 mg b.i.d.	
	n/N*	**%**
Bacteriology ITT	**N=359**	
Penicillin-resistant *S. pneumoniae* (≥2μg/mL)	10/10	(100.0)
Erythromycin Resistant *S. pneumoniae* (≥1μg/mL)	15/17	(88.2)
Beta-Lactamase Positive *H. influenzae*	12/14	(85.7)
Beta-Lactamase Positive *M. catarrhalis*	27/30	(90.0)
Beta-Lactamase Positive MSSA	15/17	(88.2)
Bacteriology PP	**N=321**	
Penicillin-resistant *S. pneumoniae* (≥2μg/mL)	9/9	(100.0)
Erythromycin Resistant *S. pneumoniae* (≥1μg/mL)	13/14	(92.9)
Beta-Lactamase Positive *H. influenzae*	10/11	(90.9)
Beta-Lactamase Positive *M. catarrhalis*	25/25	(100.0)
Beta-Lactamase Positive MSSA	15/17	(88.2)

* *n/N* = number of isolates which were eradicated or presumed eradicated / number of isolates with MIC or beta-lactamase data for the pathogen.

Note: 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 in this table.

Assessment of Treatment Failures in ABS Studies

Study 550:

In the Clinical PP population of this study, 18 patients in the Augmentin XR group and 20 patients in the levofloxacin group had a combined clinical/radiological response of failure. In both treatment groups, the majority of these patients were both clinical and radiological failures. However, there were 2/18 patients (11.1%) in the Augmentin XR group and 4/20 patients (20.0%) in the levofloxacin group who were clinical successes at test of cure but their radiological outcome was 'worse'. Thus, the combined clinical/radiological response for these patients was failure.

Study 551:

Data for patients with a bacteriological and/or combined clinical/radiological response of failure in the Bacteriology PP population of Study 551 were reviewed taking into account any pathogen MIC data and relevant clinical features. These failures could not be explained in terms of the amoxicillin/clavulanic acid MIC against the initial pathogen at screening, as the MICs were generally low. In the few cases where there was documented persistence or recurrence of the initial pathogen, the MICs for amoxicillin/clavulanic acid were low and, with one exception, had not increased between screening and the time of failure (plus or minus one dilution). The exception was a recurrent

isolate of *H. influenzae* (beta-lactamase negative) in patient 551.610.04635, in which the amoxicillin/clavulanic acid MIC increased from [redacted] µg/mL at screening to [redacted] µg/mL at test of cure.

Additional Microbiological Assessment of Augmentin XR from Combined Sinusitis/ Acute Otitis Media Pathogens

To further support the efficacy of Augmentin XR in the treatment of ABS due to PRSP (penicillin MIC of ≥2µg/mL) and macrolide-resistant *S. pneumoniae* (erythromycin MIC ≥1µg/mL), the sponsor submitted data from Study 551 combined with data from Study 536 conducted with a 14:1 suspension of Augmentin (Augmentin ES). Study 536 was conducted in pediatric patients with acute otitis media (AOM) and was been previously submitted to FDA (NDA 50-755) to support the indication of AOM due to PRSP. Similar pathogens were expected to be isolated from patients in Studies 551 and 536 since the indications are both closed system infections of the upper respiratory tract.

MO COMMENT: The division discussed and agreed to the submission of this type of combined data analysis for the indication of ABS due to PRSP (meetings of June 17, 1999 and June 7, 2000). The combining of isolates for PRSP was discussed in a previous advisory committed meeting (Moxifloxicin) where it was stated that isolates should not be combined for analysis if they are obtained from upper and lower respiratory tract infections. It was stated (Barbara Murray) that if isolates were combined from AOM and ABS, that such an approach could be acceptable, because these both represent closed space upper respiratory tract infections with similar pathophysiology and microbiology. The division did not discuss with the sponsor any details about how such a combined analysis should be performed.

Data from Study 536 are used solely to support the efficacy of Augmentin XR against PRSP and macrolide-resistant strains of *S. pneumoniae*. These data include all patients with *S. pneumoniae* who completed Study 536 on or before November 5, 1999 (i.e., the data submitted as part of Augmentin ES NDA 50-755).

The data from Study 536 are considered supportive for efficacy against PRSP and macrolide-resistant strains of *S. pneumoniae*. The T>MIC (% of 12 hour dosing interval) for a MIC of 4µg/mL was 46% following oral administration of Augmentin ES suspension at a dose of 90/6.4mg/kg/day to pediatric patients. This is similar to values obtained following oral administration of Augmentin XR to adults. The predicted efficacy from the pharmacodynamic profile of the Augmentin 14:1 suspension is similar to that of the Augmentin XR formulation, and thus the bacteriological outcome for PRSP in Study 536 may be considered as supportive of the bacteriological efficacy of Augmentin XR.

Overview of Study 536 Design and Methodology

The primary objective of Study 536 was to assess the bacteriological efficacy of Augmentin ES in children with AOM due to *S. pneumoniae* with penicillin MICs ≥2µg/mL and in children with AOM due to *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4µg/mL. The study was a multicenter, non-comparative design. Patients were treated with 10 days of Augmentin ES 90/6.4 mg/kg/day in divided doses q12h. All treated patients had a tympanocentesis procedure performed within the 24 hours before study entry in order to obtain specimens of middle ear fluid (MEF) for bacteriological evaluation. Patients from whom *S. pneumoniae* (alone or in combination with other pathogens) was isolated had a repeat tympanocentesis 4 to 6 days after start of therapy. Patients from whom other pathogens only were isolated had a repeat tympanocentesis either in instances of clinical failure, or alternatively, a few centers performed repeat tympanocentesis at Day 4-6 on all patients who had bacterial growth on initial tympanocentesis. Patients were monitored with an on-therapy visit (Day 4-6), returned for an end of treatment visit (Day 12-15), and a test of cure visit (Day 25-28).

Bacteriology Populations for Combined Sinusitis/AOM

For the purpose of the combined analysis of Studies 551 and 536, bacteriological data for the on-therapy second tympanocentesis in Study 536 (primary endpoint of Study 536) were combined with the bacteriology data for the test of cure assessment of Study 551 (primary endpoint of Study 551). The choice of a bacteriological endpoint in Study 536 was for the purpose of performing a more rigorous evaluation of the effect of Augmentin ES on the pathogens associated with AOM, as clinical resolution of symptoms has been observed even in the absence of antibiotic therapy. The key assessment of clinical response in Study 536 occurred at the end of therapy visit. Due to the high reinfection in AOM from day care settings and cross-infection from siblings, evaluation of clinical status at the end of therapy was designated as the main endpoint for determining clinical resolution of symptoms. Therefore, clinical response for the combined analysis of Studies 536 and 551 was based on data from the end of therapy visit in Study 536 and the test of cure visit in Study 551.

Because the primary bacteriological analysis in Study 536 was based on an on-therapy visit and the main clinical assessment occurred at the end of therapy visit, it was possible for patients who did not qualify for the Clinical PP population at end of therapy to be eligible for the Bacteriology PP population (on-therapy). Therefore, in order to maintain a level of population definition consistency between Studies 536 and Study 551, the sponsor's analysis combined only those patients with *S. pneumoniae* from Study 536 who met the criteria for both the Clinical PP (end of therapy) and Bacteriology PP (on-therapy) with the test of cure clinical and bacteriological data from Study 551.

The number of patients from Study 536 and Study 551 in the combined analysis are summarized in the following table for both the Bacteriology PP and ITT populations.

Bacteriology Populations in Combined Analysis: ABS Study 551 and Otitis Media Study 536

	Bacteriology PP		**Bacteriology ITT**	
ABS Study 551		**Augmentin XR**		
S. pneumoniae alone or with other pathogens	**N=104**		**N=113**	
S. pneumoniae (Penicillin MICs ≥2μg/mL), n (%)	9	(8.7)	10	(8.8)
S. pneumoniae (Erythromycin MIC ≥1μg/mL, n (%)	15	(14.4)	18	(15.9)
AOM Study 536		**Augmentin ES**		
S. pneumoniae alone or with other pathogens	**N=122**		**N=159**	
S. pneumoniae (Penicillin MICs ≥2μg/mL), n (%)	30	(24.6)	41	(25.8)
S. pneumoniae (Erythromycin MIC ≥1μg/mL, n (%)	18	(14.8)	25	(15.7)
Combined 551/536		**Augmentin XR/ES**		
S. pneumoniae alone or with other pathogens	**N=226**		**N=272**	
S. pneumoniae (Penicillin MICs ≥2μg/mL), n (%)	39	(17.3)	51	(18.8)
S. pneumoniae (Erythromycin MIC ≥1μg/mL), n (%)	33	(14.6)	43	(15.8)

Notes: N=number of patients with *S. pneumoniae* alone or with other pathogens at screening regardless of whether MIC data were available.
n (%) for *S. pneumoniae* by susceptibility to penicillin and erythromycin includes all isolates of resistant *S. pneumoniae* with MIC data.

As described in the PRSP report for Study 536 (based on patients who had completed the study by November 5, 1999), of the 521 patients who received at least one dose of Augmentin ES in Study 536, 159 presented with *S. pneumoniae* alone or with other pathogens. These 159 patients comprised the Bacteriology ITT population of Study 536 and their data were combined with the 113 patients in the Bacteriology ITT population of Study 551 who also had *S. pneumoniae* at screening, to give a total Bacteriology ITT population for the combined analysis of 272 patients. In the combined Bacteriology ITT population with *S. pneumoniae*, there were 51 patients with PRSP (10 patients from Study 551 and 41 patients from Study 536), and 43 patients with macrolide-resistant *S. pneumoniae* (18 patients from Study 551 and 25 patients from Study 536).

For the analysis of the Bacteriology PP population, 122 patients with *S. pneumoniae* alone or with other pathogens at baseline from Study 536 were combined with 104 patients from Study 551 who also had *S. pneumoniae* at screening, to give a total of 226 patients with *S. pneumoniae* in the combined analysis. In the combined Bacteriology PP population with *S. pneumoniae*, there were a total of 39 patients with PRSP (9 patients from Study 551 and 30 patients from Study 536) and 33 patients with macrolide-resistant *S. pneumoniae* (15 patients from Study 551 and 18 patients from Study 536) .

Results of Clinical and Bacteriological Efficacy in Sinusitis/AOM due to PRSP

In the combined population of patients with *S. pneumoniae* with a documented MIC for penicillin, the proportions of strains which were found to be resistant to penicillin were: 17.8% (39/219 isolates) for the Bacteriology PP population and 19.3% (51/264 isolates) for the Bacteriology ITT population.

Rates of bacteriological success for patients with PRSP in the combined sinusitis/AOM population of patients treated with Augmentin XR (Study 551) and Augmentin ES (Study 536) were high; 37/39 patients (94.9%; 95% CI: 81.4, 99.1) for the Bacteriology PP population and 48/51 patients (94.1%; 95% CI: 82.8, 98.5) for the Bacteriology ITT population. Rates of overall bacteriological eradication (eradicated and presumed eradicated) for patients with PRSP were the same as for the per patient bacteriological response for both the Bacteriology PP and Bacteriology ITT populations. The clinical success rate for patients with PRSP in the combined population was lower than for bacteriological response: 34/39 patients (87.2%; 95% CI 71.8%, 95.2%) for the Bacteriology PP population and 39/51 patients (76.5%; 95% CI 62.2%, 86.8%) for the Bacteriology ITT population.

In summary, the efficacy of Augmentin (Augmentin XR and Augmentin ES) in the treatment of PRSP in ABS and AOM is supported by the bacteriological success rate of 94.9% (37/39 patients) and the clinical success rate of 87.2% (34/39 patients) in the Bacteriology PP population of the combined 551/536 study population.

MOCOMMENT: The division has not received a similar combined analysis in prior NDA 's. It is difficult to determine how to interpret this information given the differences between the two sets of data which were combined. This includes differing endpoints, patient populations, drug formulations, study designs, and diseases.

Overall Conclusions of the Efficacy of Augmentin XR in Acute Bacterial Sinusitis

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

- In one principal controlled ABS study, Study 550, the efficacy of Augmentin XR 2000/125mg twice daily for 10 days was as good as that of levofloxacin 500mg once daily for 10 days, in terms of the combined clinical and radiological response at test of cure (primary efficacy variable).

- In one principal uncontrolled ABS study, Study 551, a high per patient bacteriological success rate (primary efficacy variable) and clinical success rate were demonstrated with Augmentin XR 2000/125mg twice daily for 10 days at test of cure.

  - Augmentin XR successfully eradicated key pathogens associated with ABS namely, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *K. pneumoniae*, *H. parainfluenzae* and MSSA.

  - All 10 patients with penicillin-resistant *S. pneumoniae* were bacteriological and clinical successes at test of cure.

  - Augmentin XR successfully eradicated macrolide-resistant isolates of *S. pneumoniae* as well as beta-lactamase producing strains of *H. influenzae*, *M. catarrhalis* and MSSA.

These data support the efficacy of Augmentin XR at a dose of 2000/125mg b.i.d. for 10 days for the treatment of ABS due to *S. pneumoniae, H. influenzae, M. catarrhalis, H. parainfluenzae* and MSSA, including beta-lactamase producing strains; and *K. pneumoniae.*

However, there is no evidence from the data submitted in this NDA demonstrating that this formulation provides any added benefit to already approved lower dosage formulations of Augmentin which are indicated for bacterial sinusitis. Activity against PRSP would have constituted such a benefit. But, it has been the division's policy that a sponsor should show activity against PRSP for more severe diseases (such as pneumonia) prior to receiving an indication for PRSP for less severe diseases (such as sinusitis). This policy developed because clinical benefit could be more clearly be demonstrated for serious infections rather than less severe infections where the treatment effect is relatively lower.

EFFICACY OF AUGMENTIN XR IN COMMUNITY ACQUIRED PNEUMONIA

Augmentin XR Clinical Program in CAP

The efficacy of Augmentin XR in CAP is demonstrated in two principal controlled clinical studies and one principal uncontrolled study.

Clinical Studies of Augmentin XR in CAP

Study	Treatment Regimen	Duration	N*	Geographic Region
Principal Controlled Studies				
546	Augmentin XR 2000/125mg b.i.d.	7 days	255	US, Europe and Mexico/Guatemala
	Augmentin 875/125mg b.i.d.	7 days	261	
556	Augmentin XR 2000/125mg b.i.d.	10 days	169	Europe, South Africa, Panama and Costa Rica
	Augmentin 1000/125mg tid	10 days	178	
Principal Uncontrolled Study				
547**	Augmentin XR 2000/125mg b.i.d.	7 days	421**	World-wide

* N refers to the number of randomized patients (N=enrolled for uncontrolled study)
** Study 547 includes efficacy data from interim analysis for patients who completed the study on or before 6/19/00, and whose data were received by SKB.

MO COMMENT: The design of all three studies was consistent with current FDA draft guidances for the study of community acquired pneumonia. Studies 546 and 556 were comparative controlled clinical studies while study 547 was an open non-comparative bacteriological study.

Principal Controlled Studies in CAP: Studies 546 and 556

Study Design and Methodology

The two principal controlled CAP studies (Studies 546 and 556) 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 Augmentin regimens used in clinical practice.

In Study 546, a 7 day course of Augmentin XR was compared with amoxicillin/clavulanate 875/125mg (7:1) b.i.d. for 7 days, which is the conventional Augmentin formulation currently used in

the US for the treatment of CAP. It was anticipated that amoxicillin/clavulanate 875/125mg b.i.d., with a NCCLS breakpoint of 2μg/mL, would provide adequate coverage for 90% of *S. pneumoniae* isolates.

In Study 556, Augmentin XR was compared with Augmentin 1000/125mg (8:1) t.i.d., which is the approved Augmentin dose regimen for CAP in France, one of the principal countries involved in the study. In France the usual prescription is 10 days treatment with Augmentin for CAP. Therefore in Study 556, a 10 day regimen of Augmentin 1000/125mg tid was compared with a 10 day regimen of Augmentin XR.

MO COMMENT: The comparator in Study 556 (Augmentin 1000/125mg –8:1) is not approved for use in the U.S. It contains more daily clavulanate (additional 125mg) and a total daily dose of amoxicillin of 3000mg (compared with the FDA approved Augmentin formulation which has 1,750 mg.)

Male and female patients (aged ≥16 years in Study 546 and aged ≥18 years in Study 556) with a clinical and radiological diagnosis of CAP, were recruited into the controlled CAP studies if they met eligibility criteria that were in agreement with FDA draft guidance. The principal entry criteria are summarized as follows:

- a chest radiograph within 48 hours before randomization or at the screening visit showing the presence of new or progressive infiltrate(s) or consolidation consistent with pneumonia,
- a fever (as defined for each study) or history of fever for the current CAP infection,
- at least one (Study 546) or two (Study 556) of the following additional signs or symptoms of CAP: - new or increased cough - purulent sputum or a change in sputum characteristics - auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation - dyspnea or tachypnea (Study 546) - in addition in Study 546, an elevated total peripheral WBC count of >10,000 cells/mm^3, or >15% immature neutrophils regardless of total peripheral WBC count, or leukopenia with total WBC count <4,500 cells/mm^3, and hypoxemia, with a PO_2 <60mmHg while patient was breathing room air,
- in Study 556, patients were to be able to provide a sputum sample (or a respiratory sample obtained by invasive means if clinically indicated).

Patients who had complicating infections, diseases, or concomitant therapy that would compromise evaluation of the study indication were excluded. Other exclusion criteria included hospital-acquired pneumonia, pneumonia with suspected atypical pathogen involvement, pneumonia of suspected viral origin (Study 556), post-obstructive pneumonia, aspiration pneumonia, cystic fibrosis, active tuberculosis, active bronchiectasis as defined in the study protocols, or active pulmonary malignancies. Patients who required parenteral antibiotic therapy or who had signs of disseminated infection were also excluded. In Study 546, patients who had received more than 24 hours treatment with any other antibacterial agent for the present episode of CAP within 7 days prior to enrolment were excluded, whereas in Study 556 patients who failed therapy with macrolides and first generation cephalosporins were allowed. Other standard exclusion criteria included the presence of renal impairment, impaired liver function and in female patients, pregnancy, lactation or inadequate birth control method.

After screening, patients eligible to receive study medication were randomly assigned to receive either Augmentin XR or the comparator Augmentin regimen in a double-blind fashion. Patients could be treated as an out-patient or in hospital depending on clinical need. Out-patients attended the clinic for three further visits to evaluate their clinical, bacteriological and radiological response to treatment. The visits were scheduled as follows: on-therapy (Day 3-5, both studies); end of therapy (Day 9-11 in Study 546 and Day 12-14 in Study 556); and test of cure (Day 28-35, both studies).

Before breaking the study blind, for the purpose of analysis the protocol-specified windows for the following assessments were extended:

- screening: Day –2 to 1
- end of therapy: Day 8-15 (Study 546) and Day 11-17 (Study 556)
- test of cure: Day 16-37 (Study 546) and Day 18-39 (Study 556)

Assessments conducted at the clinic visits included the signs and symptoms of CAP to evaluate clinical outcome and chest X-rays to evaluate radiological outcome. Sputum or invasive respiratory samples for bacteriological evaluation were collected at screening, and where possible at end of therapy and at test of cure. In the case of a patient withdrawal due to clinical failure while on therapy, a sputum sample was collected at the on-therapy visit.

In addition, blood samples for culture were obtained at screening and repeated at test of cure if positive, or if clinically indicated. Serum samples were collected at screening and repeated at test of cure visits for serological determination of *C. pneumoniae, Chlamydia psittaci, L. pneumophila* and *M. pneumoniae.* A urine sample was collected at screening for *L. pneumophila* direct antigen testing.

Assessment of Efficacy and Statistical Methodology

Efficacy Variables
The primary efficacy variable in the two principal controlled CAP studies was the clinical response (success or failure) at test of cure. 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 determined based on the changes in signs and symptoms of CAP from the screening assessment, leading first to the assignment of a clinical outcome by the investigator ie, clinical success, clinical recurrence or unable to determine. A patient's 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***
- Clinical failure at end of therapy	⇒ ***Clinical Failure***
- Unable to determine at end of therapy	⇒ ***Clinical Failure***

Clinical response was also assessed at end of therapy as a secondary endpoint. 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 clinical failure at end of therapy were carried forward to test of cure as failures. Likewise patients with a clinical outcome of Unable to Determine at end of therapy were carried forward to test of cure as failures in the ITT analyses.

For key secondary efficacy variables, the results of clinical response at end of therapy are presented as well as the results of bacteriological response at test of cure and end of therapy.

The bacteriological response for each patient was determined from the bacteriological outcome for pathogens isolated from sputum, respiratory samples from invasive procedures or blood by culture. Pathogens identified by serology (*L. pneumophila, M. pneumoniae, C. pneumoniae* or *C. psittaci*)

which are commonly associated with atypical pneumonia were not considered as initial pathogens for the purposes of including the patient in the Bacteriology ITT population.

Where both a sputum sample and an invasive respiratory sample were obtained, data from the invasive respiratory sample only were included in the database. If two isolates of the same *genus* and *species* from the same patient at the same visit were recovered, one from an invasive respiratory source and the other from blood, both isolates were analyzed regardless of MIC results. When two isolates of the same genus and species were isolated from the same sample from the same patient at the same visit or from two different samples from the same patient at the same visit, they were considered to be different strains if there was a ≥ 4-fold difference in MIC to one member of two or more antibiotic classes, and both isolates were included in the analysis.

In patients with a pre-therapy (or initial) typical pathogen but without an evaluable sample at end of therapy or test of cure (e.g. due to clinical improvement), presumed bacteriological outcome was determined on the basis of clinical response. The patient's bacteriological success combined information on initial and new typical pathogens. Patients with a bacteriological outcome of failure or presumed failure, or unable to determine (ITT only), for one or more initial typical pathogens were carried forward to test of cure as failures.

Data Sets for Analysis
Four patient populations were defined for the purposes of analyses 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 which excluded patients who violated the protocol to an extent that could affect treatment efficacy.

Patients were excluded from the PP populations only from the time that the protocol violation occurred.

The protocols for Studies 546 and 556 identified the PP population as the population for the principal analysis, with the ITT population providing confirmatory analysis. In the ISE, the results of both populations are presented and any differences between the two populations are highlighted.

Patients with a clinical outcome of Unable to Determine were excluded from the Clinical PP population. However, in the ITT analyses, clinical outcomes of Unable to Determine were classified as clinical responses of failure, representing a worst case approach.

Statistical Methodology

The two principal controlled CAP studies were designed to demonstrate that Augmentin XR was at least as good as the comparator Augmentin regimen. The planned sample size of 508 patients in Study 546 (to provide 380 clinically evaluable patients) was determined based on an underlying equivalent clinical response rate of 90%. In contrast, the planned sample size of 320 patients in Study 556 (to provide 240 clinically evaluable patients) was determined based on an underlying equivalent clinical response rate of 85% at test of cure. The lower clinical response rate anticipated in Study 556 was based on an expected higher incidence of hospitalized patients in this study as well as the inclusion of patients who had failed previous treatment with a macrolide or a first generation cephalosporin. The estimation of sample size assumed 90% power to show that the lower bound of the two-sided 95% CI for the difference in response rates (Augmentin XR minus

Augmentin comparator) was no less than the pre-defined non-inferiority limit. The non-inferiority limits were set at –10% for Study 546 and –15% for Study 556.

MO COMMENT: Although the sponsor anticipated a lower clinical response rate in Study 556, the clinical PP test of cure success rates for both study arms were >90% and an evaluation of the severity of illness via modified Fine scores revealed that the majority of the enrolled population did not have moderate to severe CAP (Risk Class IV-V).

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. The studies were not designed to demonstrate non-inferiority for secondary efficacy variables.

Disposition and Characteristics of the Study Populations

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

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

A similar number of patients withdrew from Studies 546 and 556; 59 patients (11.5%) withdrew from Study 546 (Augmentin XR: 28/255, 11.0%, Augmentin 875/125mg: 31/259, 12.0%), and 51 patients (14.8%) withdrew from Study 556 (Augmentin XR: 28/169, 16.6%, Augmentin 1000/125mg: 23/175, 13.1%). 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. The numbers withdrawn due to insufficient therapeutic effect were too small in each study to allow reliable comparisons to be made.

The disposition of patients in the two principal controlled CAP studies, including reasons for withdrawal (at any time of the study), are tabulated by treatment group in the following table.

Patient Disposition: CAP Principal Controlled Studies 546 and 556

	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	
Randomized	255		261		169		178	
Received Study Medication (ITT)	255		259		169		175	
Completed Study	227		228		141		152	
Reason for Withdrawal (ITT), n (%):								
Adverse Experience	10	(3.9)	19	(7.3)	9	(5.3)	7	(4.0)
Insufficient Therapeutic Effect	2	(0.8)	1	(0.4)	5	(3.0)	5	(2.9)
Protocol Deviation *	2	(0.8)	1	(0.4)	6	(3.6)	5	(2.9)
Lost to Follow-Up	11	(4.3)	10	(3.9)	6	(3.6)	4	(2.3)
Other Reason**	3	(1.2)	0	-	2	(1.2)	2	(1.1)
Total Withdrawn, n (%)	28	(11.0)	31	(12.0)	28	(16.6)	23	(13.1)
Populations for Analysis								
Clinical PP at End of Therapy	221		219		129		119	
Clinical PP at Test of Cure	204		204		118		114	
Bacteriology ITT	39		30		44		47	
Bacteriology PP at End of Therapy	33		26		33		34	
Bacteriology PP at Test of Cure	32		26		32		32	

* Including non-compliance

** Other reasons for withdrawal, as determined by the investigator, included:
Study 546 – 'refused clinical evaluation at Visit 4', 'patient withdrew consent' and 'exacerbation of chronic diarrhea'.
Study 556 – 'patient refused to continue' (one patient), 'patient discontinued' (one patient) and 'patient withdrew consent' (two patients).

Protocol Violations

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. The incidence of exclusions from the Bacteriology PP populations was similar between the treatment groups in both studies. In Study 546, 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, and lack of medication compliance. In Study 556, the major reasons for exclusion from the Clinical PP population at test of cure in both treatment groups were that the patient did not have CAP, lack of medication compliance and a clinical outcome of Unable to Determine. It is noted that in Study 556, to confirm eligibility, all screening chest X-rays were reviewed by an independent expert review committee before breaking the study blind, resulting in a greater proportion of patients than expected who were excluded for not having radiologically confirmed CAP: 21 patients (12.4%) in the Augmentin XR group and 27 patients (15.4%) in the Augmentin 1000/125mg group.

A summary of the proportions 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.

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Number (%) of Patients Excluded From the Clinical and Bacteriology PP Populations – CAP Principal Controlled Studies 546 and 556

		Study 546 Augmentin XR 2000/125mg b.i.d.		Augmentin 875/125mg b.i.d.		Study 556 Augmentin XR 2000/125mg b.i.d.		Augmentin 1000/125mg tid	
ITT Population		**N=255**		**N=259**		**N=169**		**N=175**	
Clinical PP	**Visit**								
n (%) excluded	End of Therapy	34	(13.3)	40	(15.4)	40	(23.7)	56	(32.0)
	Test of Cure	51	(20.0)	55	(21.2)	51	(30.2)	61	(34.9)
Bacteriology ITT		**N=39**		**N=30**		**N=44**		**N=47**	
Bacteriology PP	**Visit**								
n (%) excluded	End of Therapy	6	(15.4)	4	(13.3)	11	(25.0)	13	(27.7)
	Test of Cure	7	(17.9)	4	(13.3)	12	(27.3)	15	(31.9)

Demographic and Baseline Characteristics

In both studies, the two treatment groups were generally well matched with respect to demographic characteristics and there were no major differences evident between the ITT population and the Clinical PP populations in each of the studies.

The demographic and baseline characteristics of the populations with CAP in the two principal controlled studies are shown in the following table (Clinical PP population).

Demographic Characteristics and Mortality Risk: CAP Principal Controlled Studies 546 and 556 (Clinical PP Test of Cure Population)

Baseline/Demographic Characteristic	Study 546 Augmentin XR 2000/125mg b.i.d. N=204		Augmentin 875/125mg b.i.d. N=204		Study 556 Augmentin XR 2000/125mg b.i.d. N=118		Augmentin 1000/125mg tid N=114	
Gender, n (%)								
Male	102	(50.0)	104	(51.0)	63	(53.4)	66	(57.9)
Female	102	(50.0)	100	(49.0)	55	(46.6)	48	(42.1)
Race, n (%)								
White	171	(83.8)	182	(89.2)	108	(91.5)	110	(96.5)
Black	16	(7.8)	6	(2.9)	3	(2.5)	3	(2.6)
Oriental	3	(1.5)	1	(0.5)	1	(0.8)	0	-
Other*	14	(6.9)	15	(7.4)	6	(5.1)	1	(0.9)
Age (yrs)								
Mean (SD)	51.3 (17.2)		52.2 (17.6)		57.8 (19.1)		57.0 (19.8)	
Range	17-88		16-91		19-92		18-89	
CAP Mortality Risk, n (%)**								
Low	-		-		32	(27.1)	26	(22.8)
Moderate	-		-		11	(9.3)	6	(5.3)
High	-		-		2	(1.7)	0	-
Unknown†	-		-		73	(61.9)	82	(71.9)
Hospitalized, n (%)	8	(3.9)	9	(4.4)	88	(74.6)	89	(78.1)

* Other included patients described as: Study 546 - Hispanic (27 patients), Portuguese (1 patient) and Asian (1 patient); Study 556: 'Black half breed' (one patient), Hispanic (6 patients).

** The mortality risk of patients was assessed in Study 556 according to the risk classes (I, II, III, IV and V) published by Fine et al. Low Risk comprised classes I, II and III, Moderate Risk class IV, and High Risk Class V.

† Patients where at least one data point used in the Fine scoring system was missing and hence mortality risk could not be determined.

MO COMMENT: The demographic characteristics and mortality risk for Studies 546 and 556 were equally well matched for the ITT populations.

The demographic characteristics of the ITT populations differed slightly between the two studies. In Study 546, the mean age of patients was 52.0 years in the Augmentin XR group and 52.5 years in the Augmentin 875/125mg group compared with 57.3 years in the Augmentin XR group and 56.9 years in the Augmentin 1000/125mg group of Study 556. The majority of patients were white in both studies but the proportion was less overall in Study 546 (84.4%, 434/514) compared with Study 556 (93.3%, 321/344). In Study 546 approximately half of the patients were male (Augmentin XR: 51.0%; Augmentin 875/125mg: 49.0%), while in Study 556 there was a slightly higher proportion of males (Augmentin XR: 55.0%; Augmentin 1000/125mg: 58.9%). Similar observations were made for the Clinical PP test of cure population.

Only a small proportion of the ITT population in Study 546 was hospitalized at screening for CAP (12 patients in each of the treatment groups). In Study 556, as expected, a much greater proportion of patients were hospitalized, 71.5% (246/344). There was also a slightly smaller proportion of hospitalized patients in the Augmentin XR group (68.6%) than in the Augmentin 1000/125mg group (74.3%) in Study 556.

MO COMMENT: There was a greater proportion of patients in Study 556 who were hospitalized, however, upon review, this appears to be the result of differing admission practices in Europe as compared to the U.S. It does not appear to be related to enrollment of patients with more severe disease. No ~~~~~ for Augmentin were used in these studies, so patients were hospitalized, and yet were not thought to be sick enough to ~~~~ antibiotics.

In the ITT population of Study 546, with the exception of two patients in the Augmentin XR group and two patients in the Augmentin 875/125mg group, all patients had radiographic evidence consistent with a diagnosis of CAP. In the ITT population of Study 556, 88.2% of patients in the Augmentin XR group and 87.4% of patients in the Augmentin 1000/125mg group had radiographic evidence consistent with a diagnosis of CAP at screening. All patients in the Clinical PP population of each study had radiographic evidence of CAP.

In both studies, there were no marked differences between the treatment groups in either the ITT or Clinical PP populations, in the proportions of patients with clinical characteristics of CAP at screening (including fever, WBC count, sputum, cough, dyspnea, tachypnea, hypoxemia, pleuritic chest pain and auscultatory findings).

In Study 556, patients were assessed by the Sponsor prior to database release or any data evaluation, according to the risk classes published by Fine *et al.* Patients were assigned to one of five classes (I, II, III, IV and V) with respect to risk of death within 30 days, on the basis of a continuous points score. A prediction rule assigned points based on age and the presence of co-existing disease, abnormal vital signs and abnormal laboratory findings at presentation. Based on the risk class, patients were classified with a mortality risk of low, moderate or high. Risk class and mortality risk were only calculated for patients who had data for systolic blood pressure and pH of arterial blood and either an arterial blood gas or pulse oximetry. In the ITT population, a total of 225 patients (65.4%) were classified as 'unknown' since they did not have data for one or more of these measurements and mortality risk could not be determined.

For the majority of patients, the risk class and mortality risk were unknown (63.9% in the Augmentin XR group and 66.9% in the Augmentin 1000/125mg group). Similar proportions of patients in each of the treatment groups were of low mortality risk. The proportions of patients with moderate risk were 10.7% in the Augmentin XR group and 7.4% in the Augmentin 1000/125mg group. Only two patients, both in the Augmentin XR group, were in the high mortality risk category.

Bacteriology at Screening

Overall, 69 patients (13.4%) in Study 546 and 91 patients (26.5%) in Study 556 had at least one typical pathogen isolated at screening (all sources). In Study 546, the inclusion criteria did not stipulate requirement for a sputum or respiratory sample at screening and this may have contributed to the smaller number of patients in this study with baseline pathogen data.

The incidences of specific key pathogens were similar between treatment groups in both studies. In both studies, *S. pneumoniae* and *H. influenzae* were the most prevalent pathogens; in Study 546 these two