

CONCLUSIONS

BRL-025000/546 is a randomized, multicentre, double-blind, double-dummy, parallel group study was designed to assess the clinical and bacteriological 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 patients with clinically and radiologically confirmed CAP due to susceptible strains of common pathogens, including penicillin-resistant strains of *S. pneumoniae* (PRSP) and beta-lactamase producing strains of *H. influenzae* and *M. catarrhalis*. Only two PRSP patients participated in this study.

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

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

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

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

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STUDY BRL-025000/556

INTRODUCTION

Study Objectives

Primary: To demonstrate that oral Augmentin XR 2000/125mg twice daily for 10 days was at least as effective clinically as oral Augmentin 1000/125mg three times daily for 10 days in the treatment of CAP in adults.

Secondary: To evaluate the bacteriological efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days and oral Augmentin 1000/125mg three times daily for 10 days in the treatment of CAP in adults.

METHODOLOGY

Study Design

This was a randomized, multicentre, double-blind, double-dummy, parallel group, Phase III study to assess the clinical and bacteriological efficacy and safety of oral Augmentin XR in comparison to oral Augmentin 1g for the treatment of CAP in adults. The study was designed to enroll approximately 320 patients, to provide approximately 240 clinically evaluable patients (120 per treatment arm).

The study was carried out at 77 centres in various countries. In Costa Rica (1 centre), France (58 centres), Hungary (3 centres), Lithuania (7 centres), Panama (1 centre), Poland (6 centres) and South Africa (1 centre).

Patients with CAP suspected to be due to typical bacteria, who fulfilled the entry criteria and had given written, dated informed consent were randomized in a double-blind fashion (1:1 ratio) to receive either Oral Augmentin XR 2000/125mg tablets twice daily and oral Augmentin-placebo sachets three times daily for 10 days or Oral Augmentin 1000/125mg sachets three times daily and oral Augmentin XR-placebo tablets twice daily for 10 days.

Primary Efficacy Variable

The primary efficacy variable was the clinical response at the test of cure visit (Visit 4).

For patients who were clinical successes at the end of therapy visit, the investigator determined the patient's clinical outcome at test of cure. The patient's clinical response at test of cure was then defined as follows.

- **Success:** The patient's clinical outcome at the test of cure visit was 'test of cure clinical success'.
- **Failure:** The patient's clinical outcome at the test of cure visit was 'clinical recurrence' or 'unable to determine', or the patient's clinical outcome at the end of therapy visit was 'clinical failure' or 'unable to determine'.

Patients whose clinical outcome was 'unable to determine' were excluded from the Clinical PP population. Patients who were clinical failures at end of therapy and who subsequently became protocol violators at the test of cure visit were included as failures in the Clinical PP population at test of cure because they had satisfied the criteria for being included in the test of cure failure group prior to violating the protocol.

Secondary Efficacy Variables

The secondary efficacy variables were as follows:

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

Statistical Reviewer's Comments:

Testing the equivalence of treatment difference with respect to the efficacy variables were assessed based on a two-tailed 95% confidence interval of the difference in cure rates and a lower bound of no less than -10% for the confidence interval would be used for the primary efficacy analysis.

The primary efficacy analysis will be based on the clinically evaluable (PP) and the ITT or the Bacteriological ITT/Modified Intent-to-Treat (MITT) populations.

Patient Disposition

The numbers of patients who were randomized, received study medication and completed the study, together with the numbers of patients eligible for the various ITT and PP populations are given in Table 1.

Table 1: Patient Disposition (All Randomized Patients, Sponsor' Table)

Population	Treatment Group	
	Augmentin XR 2000/125mg bid	Augmentin 1000/125mg tid
	n	n
Randomized	169	178
Received Study Medication (ITT/ Safety)	169	175
Completed Study	141	152
Clinical PP End of Therapy	129	119
Clinical PP Test of Cure	118	114
Bacteriology ITT	44	47
Bacteriology PP End of Therapy	33	34
Bacteriology PP Test of Cure	32	32

Statistical Reviewer's Comments:

In total, 347 patients were randomized to study treatment; 169 were randomized to receive Augmentin XR and 178 to receive Augmentin 1g. The Bacteriology ITT population comprised the 91 patients in the ITT population (44 in the Augmentin XR group and 47 in the Augmentin 1g group) who had at least one typical pathogen isolated at screening.

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

Country	Treatment Group			
	Augmentin XR 2000/125mg bid N=169		Augmentin 1000/125mg tid N=175	
	R	C	R	C
Costa Rica	4	3	3	3
France	86	70	96	77
Hungary	9	8	10	8
Lithuania	41	36	38	37
Panama	2	1	1	1
Poland	27	23	26	25
South Africa	0	0	1	1
Total	169	141	175	152

Sponsor's Table

R = randomized; C = completed.

Table 3: Number (%) of Patients Withdrawn from the Study by Reason for Withdrawal (ITT Population)

Reason for Withdrawal	Treatment Group			
	Augmentin XR 2000/125mg bid N=169		Augmentin 1000/125mg tid N=175	
	n	(%)	n	(%)
COMPLETED STUDY*	141	(83.4)	152	(86.9)
Reason for Withdrawal				
Adverse Experience	9	(5.3)	7	(4.0)
Insufficient Therapeutic Effect	5	(3.0)	5	(2.9)
Protocol Deviation (Including Non-Compliance)	6	(3.6)	5	(2.9)
Lost to Follow-Up	6	(3.6)	4	(2.3)
Other**	2	(1.2)	2	(1.1)
TOTAL WITHDRAWN	28	(16.6)	23	(13.1)

Sponsor's Table

* Patients were considered to have completed the study if they had taken study medication as directed during the 10 day treatment period and attended all specified visits.

** Other reasons for withdrawal as determined by the investigator, were 'patient refused to continue' (one patient), 'patient discontinued' (one patient) and 'patient withdrew consent' (two patients).

Statistical Reviewer's Comments:

In the ITT population, 293 patients completed the study; 141 (83.4%) in the Augmentin XR group and 152 (86.9%) in the Augmentin 1g group. The proportions of patients completing, and withdrawing from the study were similar in the two treatment groups. The most frequent reason for withdrawal in both treatment groups was adverse experience: 9 (5.3%) patients in the Augmentin XR group and 7 (4.0%) patients in the Augmentin 1g group. The proportions of patients who withdrew from the study and the proportions withdrawn due to adverse experiences and insufficient therapeutic effect were compared between treatment groups.

Demographic and Baseline Characteristics

The demographic characteristics of the ITT test of cure population is summarized in Table 4.

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Table 4: Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group	
	Augmentin XR 2000/125mg bid N=169	Augmentin 1000/125mg tid N=175
Gender n(%)		
Male	93 (55.0)	103 (58.9)
Female	76 (45.0)	72 (41.1)
Age (yr)		
Mean (SD)	57.3 (18.6)	56.9 (19.1)
Range	19 - 92	18 - 89
Race n(%)		
White	156 (92.3)	165 (94.3)
Black	5 (3.0)	4 (2.3)
Oriental	1 (0.6)	1 (0.6)
Other*	7 (4.1)	5 (2.9)
Weight (kg)		
Mean (SD)	68.6 (15.4)	71.2 (15.1)
Range	35 - 126	34 - 120
Height (cm)**		
Mean (SD)	166.8 (9.7)	168 (10.2)
Range	135 - 190	140 - 198
Smoking History n(%)		
Current Smoker	49 (29.0)	44 (25.1)
Ever Smoked	83 (49.1)	80 (45.7)
Smoking Pack Years:		
0	86 (50.9)	95 (54.3)
>0 - 10	28 (16.6)	27 (15.4)
>10 - 20	19 (11.2)	19 (10.9)
>20 - 30	18 (10.7)	13 (7.4)
>30	17 (10.1)	19 (10.9)
Unknown	1 (0.6)	2 (1.1)
In-patient n(%)	116 (68.6)	130 (74.3)

* The other races, as recorded verbatim by the investigator, were Augmentin XR: Black half breed (one patient), Hispanic (6 patients); Augmentin 1g: North African (one patient), Hispanic (4 patients).

** Height was not recorded for one patient in the Augmentin XR group and two patients in the Augmentin 1g group.

Statistical Reviewer's Comments:

In the ITT population, there were no major differences observed between the two treatment groups with respect to demographic characteristics. There was a slightly higher proportion of males than females in both treatment groups (in the ITT population: 55.0%:45.0% in the Augmentin XR group and 58.9%:41.1% in the Augmentin 1g group). The majority of patients were white. The mean age was 57.3 years in the Augmentin XR group and 56.9 years in the Augmentin 1g group. In the ITT population, 246/344 (71.5%) patients were hospitalised. There

was a slightly smaller proportion of in-patients in the Augmentin XR group (68.6%) than in the Augmentin 1g group (74.3%).

Table 5: Number (%) of Patients with Clinical Characteristics of CAP at Screening (ITT Population)

Clinical Characteristic	Treatment Group			
	Augmentin XR 2000/125mg bid N=169		Augmentin 1000/125mg tid N=175	
	n	(%)	n	(%)
Fever* or History of Fever	169	(100.0)	175	(100.0)
Dehydration	34	(20.1)	34	(19.4)
Altered Total WBC Count	92	(54.4)	92	(52.6)
Sputum				
Purulent Sputum	143	(84.6)	147	(84.0)
Change in Characteristics	95	(56.2)	95	(54.3)
New or Increased Cough	164	(97.0)	171	(97.7)
Cough				
None	3	(1.8)	4	(2.3)
Mild	29	(17.2)	34	(19.4)
Moderate	110	(65.1)	99	(56.6)
Severe	27	(16.0)	38	(21.7)
Dyspnoea				
None	34	(20.1)	38	(21.7)
Mild	62	(36.7)	59	(33.7)
Moderate	57	(33.7)	64	(36.6)
Severe	16	(9.5)	14	(8.0)
Tachypnoea				
None	44	(26.0)	56	(32.0)
Mild	74	(43.8)	63	(36.0)
Moderate	46	(27.2)	46	(26.3)
Severe	5	(3.0)	10	(5.7)
Hypoxaemia				
None	81	(47.9)	90	(51.4)
Mild	49	(29.0)	45	(25.7)
Moderate	25	(14.8)	30	(17.1)
Severe	14	(8.3)	10	(5.7)
Pleuritic Chest Pain				
None	65	(38.5)	68	(38.9)
Mild	29	(17.2)	37	(21.1)
Moderate	52	(30.8)	48	(27.4)
Severe	23	(13.6)	22	(12.6)
Chills	109	(64.5)	119	(68.0)
Sudden Onset of Symptoms (<48h)	124	(73.4)	136	(77.7)
Auscultatory Findings				
Rales	157	(92.9)	156	(89.1)
Pulmonary Consolidation**	125	(74.0)	121	(69.1)

Sponsor's Table

* Fever was defined in the protocol as oral temperature >38°C, tympanic temperature of >38°C or rectal temperature of >38.5°C.

** Dullness on percussion, bronchial breath sounds or egophony.

Statistical Reviewer's Comments:

All patients in the ITT population had either a current fever or history of fever on entry into the study, with at least 19% of patients in both treatment groups showing signs of dehydration. A slightly lower proportion of patients in the Augmentin XR group had chills (64.5%) than in the Augmentin 1g group (68.0%). The proportion of patients with moderate or severe cough; 81.1% (137/169 patients) in the Augmentin XR group and 78.3% (137/175 patients) in the Augmentin 1g group. A slightly higher proportion of patients in the Augmentin XR group had a moderate cough (65.1%) than in the Augmentin 1g group (56.6%). The proportion of patients with severe cough was lower in the Augmentin XR group (16.0%) than in the Augmentin 1g group (21.7%). The proportions of patients who had one or more 'severe' characteristic of CAP were; (12/169, 7.1%) patients in the Augmentin XR group and (18/175, 10.3%) patients in the Augmentin 1g group.

Table 6: Number (%) of Patients with Key Typical Pathogens Associated with CAP at Screening from Sputum, Respiratory Sample or Blood (Bacteriology ITT Population)

Pre-Therapy Pathogen	Treatment Group			
	Augmentin XR 2000/125mg bid N=44		Augmentin 1000/125mg tid N=47	
	n	(%)	n	(%)
<i>S. pneumoniae</i>	23	(52.3)	22	(46.8)
<i>H. influenzae</i>	9	(20.5)	15	(31.9)
<i>H. parainfluenzae</i>	2	(4.5)	3	(6.4)
<i>M. catarrhalis</i>	3	(6.8)	2	(4.3)
<i>K. pneumoniae</i>	3	(6.8)	1	(2.1)
MSSA*	2	(4.5)	3	(6.4)
<i>E. coli</i>	1	(2.3)	3	(6.4)

Sponsor's Table

Note Some patients may have had more than one pathogen.

* One further patient in each treatment group had a Methicillin-resistant *Staphylococcus aureus* (MRSA) isolated.

Statistical Reviewer's Comments:

In the Bacteriology ITT population the most prevalent typical pathogens in both the Augmentin XR and Augmentin 1g groups were *S. pneumoniae*, (23, 52.3% and 22, 46.8%, respectively) and *H. influenzae* (9, 20.5% and 15, 31.9%, respectively). In the Bacteriology ITT population *M. catarrhalis* was isolated from (3, 6.8%) of patients in the Augmentin XR group and (2, 4.3%) patients in the Augmentin 1g group.

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RESULTS

EFFICACY

Table 7: Clinical Response at Test of Cure (Clinical PP Test of Cure and ITT Populations)

Clinical Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Augmentin 1000/125mg tid
Clinical PP Test of Cure Population	N=118	N=114
Success n (%)	108 (91.5)	106 (93.0)
Failure n (%)	10 (8.5)	8 (7.0)
Clinical Failure at End of Therapy	9 (7.6)	8 (7.0)
Clinical Recurrence at Test of Cure	1 (0.8)	0
95% CI	-8.3, 5.4	
ITT Population	N=169	N=175
Success n (%)	137 (81.1)	150 (85.7)
Failure n (%)	32 (18.9)	25 (14.3)
Clinical Failure at End of Therapy	16 (9.5)	12 (6.9)
Clinical Recurrence at Test of Cure	3 (1.8)	0
Unable to Determine	13 (7.7)	13 (7.4)
95% CI	-12.5, 3.2	

Statistical Reviewer's Comments:

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

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**Table 8: Per Patient Bacteriological Response at Test of Cure
(Bacteriology PP Test of Cure and Bacteriology ITT Populations)**

Bacteriological Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Augmentin 1000/125mg tid
Bacteriology PP Test of Cure Population	N=32	N=32
Success n(%)	29 (90.6)	27 (84.4)
Failure n(%)	3 (9.4)	5 (15.6)
Treatment Difference % (Augmentin XR – Augmentin 1g)	6.3	
95% CI	-9.9, 22.4	
Bacteriology ITT Population	N=44	N=47
Success n(%)	37 (84.1)	36 (76.6)
Failure* n(%)	7 (15.9)	11 (23.4)
Treatment Difference % (Augmentin XR – Augmentin 1g)	7.5	
95% CI	-8.7, 23.7	

* Includes three patients in the Augmentin XR group and 4 patients in the Augmentin 1g group who were excluded from the Bacteriology PP test of cure population because of a bacteriological outcome of unable to determine.

Statistical Reviewer's Comments:

The bacteriological success rate at test of cure in the Bacteriology PP test of cure population was 90.6% in the Augmentin XR group and 84.4% in the Augmentin 1g group. Success rates in the Bacteriology ITT population were 84.1% and 76.6% in the respective treatment groups. Although it meets the non-inferiority limit, it should be noted that the numbers of patients in the Bacteriology PP and Bacteriology ITT populations were too small to draw any strong and meaningful conclusions.

**Table 9: Clinical Response at Test of Cure for Bacteraemic Patients
(Bacteriology PP Test of Cure and ITT Populations)**

	Treatment Group			
	Augmentin XR 2000/125mg bid		Augmentin 1000/125mg tid	
	n/N*	(%)	n/N*	(%)
Bacteriology PP Test of Cure Population	N=32		N=32	
Success	3/3	(100.0)	4/5	(80.0)
Failure	0/0		1/5	(20.0)
Bacteriology ITT Population	N=44		N=47	
Success	3/3	(100.0)	4/8	(50.0)
Failure	0/0		4/8	(50.0)

Statistical Reviewer's Comments:

In the Bacteriology PP population at the test of cure assessment, there were three bacteraemic patients in the Augmentin XR group and all of whom were clinical and bacteriological successes and in the Bacteriology ITT population, out of 8 patients in the Augmentin XR group, 4/8 (50%) and out of 5 patients in the Augmentin 1g group, 4/5 (80.0%) were clinical and bacteriological successes. Any meaningful conclusions could not be drawn since numbers of bacteraemic patients in these populations were too small.

SAFETY

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

Table 10: Number (%) of Patients with the Most Frequently Reported Adverse Experiences (≥2% of Patients)

Preferred Term	Treatment Group			
	Augmentin XR 2000/125mg bid N=169		Augmentin 1000/125mg tid 175	
	n	(%)	n	(%)
Patients With at Least One AE	81	(47.9)	94	(53.7)
Diarrhoea	22	(13.0)	17	(9.7)
Insomnia	7	(4.1)	7	(4.0)
Pneumonia	6	(3.6)	4	(2.3)
Abdominal Pain	5	(3.0)	7	(4.0)
Bronchitis	5	(3.0)	1	(0.6)
Headache	4	(2.4)	4	(2.3)
Herpes Simplex	4	(2.4)	2	(1.1)
Respiratory Disorder	4	(2.4)	1	(0.6)
Moniliasis	3	(1.8)	6	(3.4)
Nausea	3	(1.8)	5	(2.9)
Fungal Infection	2	(1.2)	4	

Sponsor's Table

Statistical Reviewer's Comments:

During the interval on-therapy plus 30 days post-therapy, the incidence of patients reporting with at least one AE was 47.9 % in the Augmentin XR group and 53.7% of patients in the Augmentin 1g group. The most frequently reported adverse experience in both treatment groups was diarrhoea (13.0% in the Augmentin XR group and 9.7% in the Augmentin 1g group).

Adverse Experiences by Relationship to Study Medication

The numbers (%) of patients with the most frequently reported (ie, occurring in at least 1% of patients in either treatment group) suspected or probably related AEs (there were no AEs of unknown causality) are given in Table 11.

Table 11: Number (%) of Patients with the Most Frequently Reported Adverse Experiences with a Suspected or Probable Relationship to Study Medication (≥1% of Patients)

	Treatment Group			
	Augmentin XR 2000/125mg bid N=169		Augmentin 1000/125mg tid N=175	
	n	(%)	n	(%)
Patients With at Least One AE with Suspected or Probable Relationship	31	(18.3)	42	(24.0)
Diarrhoea	21	(12.4)	15	(8.6)
Moniliasis	3	(1.8)	4	(2.3)
Abdominal Pain	2	(1.2)	2	(1.1)
Dyspepsia	2	(1.2)	3	(1.7)
Fungal Infection	2	(1.2)	3	(1.7)
Nausea	2	(1.2)	3	(1.7)
SGPT Increased	2	(1.2)	2	(1.1)
Alkaline Phosphatase Increased	1	(0.6)	2	(1.1)
Hepatocellular Damage	0		2	(1.1)
Vomiting	0		2	(1.1)

Sponsor's Table

Statistical Reviewer's Comments:

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

Deaths

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

CONCLUSIONS

This was a randomised, multicentre, double-blind, double-dummy, parallel group study to assess the clinical and bacteriological efficacy and safety of oral Augmentin XR 2000/125mg twice daily in comparison to oral Augmentin 1000/125mg three times daily for 10 days for the treatment of community acquired pneumonia in adult patients. A total of 344 patients received study medication, 169 in the Augmentin XR group and 175 in the Augmentin 1g group.

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

The bacteriological success rate at test of cure in the Bacteriology PP test of cure population was 90.6% in the Augmentin XR group and 84.4% in the Augmentin 1g group. Success rates in the Bacteriology ITT population were 84.1% and 76.6% in the respective treatment groups. Although it meets the non-inferiority limit, it should be noted that the numbers of patients in the Bacteriology PP and Bacteriology ITT populations were too small to draw any meaningful conclusions.

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

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

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STUDY BRL-025000/547

INTRODUCTION

Study Objectives

Primary: The primary objective of the study was to evaluate the bacteriological efficacy of oral Augmentin XR 2000/125mg twice daily for 7 days in the treatment of CAP in adults.

Secondary: The secondary objective of the study was to evaluate the clinical efficacy and the safety of oral Augmentin XR 2000/125mg twice daily for 7 days in the treatment of CAP in adults.

METHODOLOGY

Study Design

This is an ongoing, open, non-comparative, multicentre study to assess the bacteriological and clinical efficacy and safety of oral Augmentin XR 2000/125mg in adult patients with CAP. The study was designed to enroll approximately 1200 patients, with this interim analysis being conducted after approximately a third of the patients had been enrolled. In studies of a similar design, only 14% of recruited patients had an evaluable *S. pneumoniae* isolate, of which 6.5% of the *S. pneumoniae* isolates were penicillin resistant ($MIC \geq 2$ ug/mL, in accordance with NCCLS). Therefore, in order to obtain at least 10 penicillin-resistant isolates of *S. pneumoniae*, it was anticipated that approximately 1200 patients would be required. Recruitment will continue until a sufficient number of patients have been enrolled with community acquired pneumonia due to penicillin-resistant *S. pneumoniae*.

The study was conducted at 77 centres in 12 countries: China (6 centres), Costa Rica (1 centre), Czech Republic (3 centres), Ireland (2 centres), Mexico (2 centres), Philippines (2 centres), Poland (6 centres), Russia (6 centres), South Africa (8 centres), Thailand (1 centre), Turkey (2 centres) and USA (38 centres).

Patients were instructed to take two Augmentin XR 1000/62.5mg tablets twice daily (two tablets approximately every 12 hours) for 7 days. Study medication was to be taken at the start of a meal. Patients were encouraged to drink fluids liberally to avoid dehydration.

All patients were to take at least one dose of study medication on Day 0. Therefore, regardless of the time of enrolment on Day 0, each patient was to take two tablets of Augmentin XR. If the patient took only one dose (two tablets) of Augmentin XR on Day 0, the remaining dose (one out of two tablets) was to be taken on the last day of therapy.

Primary Efficacy Variable

The primary efficacy variable was the bacteriological response (success or failure) at the test of cure visit (Visit 4).

Secondary Efficacy Variables

Bacteriological response (success or failure) at the end of therapy visit (Visit 3)

Clinical response (success or failure) at the test of cure visit (Visit 4)

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

Target Sample Size

According to sponsor, based on previous experience in a study of similar design, only 14% of recruited patients had an evaluable *S. pneumoniae* isolate, of which 6.5% of the *S. pneumoniae* isolates were penicillin-resistant (MIC \geq 2ug/mL). Therefore, in order to obtain sufficient number of penicillin-resistant isolates of *S. pneumoniae*, the recruitment was planned to continue until a enough patients had been enrolled with community acquired pneumonia due to penicillin-resistant *S. pneumoniae*.

Statistical Reviewer's Comments:

The study 547 includes efficacy data from an interim analysis of patients who completed the study on or before June 19, 2000. The primary efficacy analysis will be based on the bacteriological evaluable (PP) and the ITT or the Bacteriological ITT populations.

Patient Disposition

The numbers of patients who were enrolled, received at least one dose of study medication (ie the ITT/safety population) and completed the study, together with the numbers of patients eligible for the various ITT and PP populations (Table 1).

Table 1 Patient Disposition (All Enrolled Patients)

Population	Augmentin XR 2000/125mg bid	
	n	
Enrolled	421	
Received Study Medication (ITT/Safety)	420	
Completed Study	369	
Clinical PP End of Therapy	360	
Clinical PP Test of Cure	333	
Bacteriology ITT	142	
Bacteriology PP End of Therapy	127	
Bacteriology PP Test of Cure	119	

A total of 421 patients were enrolled into this study and had completed all their study visits by the cut-off date for the interim analysis of 19 June 2000 and their data had been received by SB. Of these 421 patients, 420 patients received study medication and were therefore included in the ITT population. One patient (547.045.06579) was enrolled into the study but did not receive study medication and was treated with intravenous Augmentin instead. This patient was

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

Table 2 Demographic Characteristics (ITT and Bacteriology ITT Populations)

Demographic Characteristic	Augmentin XR			
	ITT N=420		2000/125mg bid Bacteriology ITT N=142	
Gender n(%)				
Male	236	(56.2)	94	(66.2)
Female	184	(43.8)	48	(33.8)
Age (yr)				
Mean (SD)	49.4 (18.8)		45.8 (18.6)	
Range	16 – 93		16 – 88	
Race n(%)				
White	274	(65.2)	107	(75.4)
Black	30	(7.1)	11	(7.7)
Oriental	68	(16.2)	14	(9.9)
Other	48*	(11.4)	10**	(7.0)
Weight (kg)				
Mean (SD)	73.1 (20.8)		72.9 (18.3)	
Range	26 – 150.9		34 – 132.5	
Height (cm) †				
Mean (SD)	168.2 (11.2)		170.5 (10.1)	
Range	136 – 203.2		141 – 200.7	
Smoking History n(%)				
Current Smoker	122	(29.0)	55	(38.7)
Ever Smoked	214	(51.0)	80	(56.3)
Smoking Pack Years:				
0	206	(49.0)	62	(43.7)
>0 – 10	89	(21.2)	29	(20.4)
>10 – 20	35	(8.3)	16	(11.3)
>20 – 30	30	(7.1)	12	(8.5)
>30	58	(13.8)	22	(15.5)
Unknown	2	(0.5)	1	(0.7)
In-Patient at screening n(%) ††	149	(35.5)	60	(42.3)

* The other races, as recorded by the investigator, were Hispanic (30 patients), mixed race (17 patients) and Indian (1 patient)

** The other races, as recorded by the investigator, were Hispanic (5 patients) and mixed race (5 patients)

† Height was missing for 6 patients in the ITT population and for 2 patients in the Bacteriology ITT population

†† For one patient in the ITT population in-patient status was unknown

Statistical Reviewer's Comments:

Comparing the ITT and Bacteriological ITT populations, the mean age of patients in the ITT population was 49.4 years, and the majority of patients were white (65.2%). In the ITT population 56.2% of patients were male and 29.0% were current smokers. In the Bacteriology ITT population the mean age of patients was 45.8 years, 75.4% of patients were white, 66.2% were male and 38.7% were current smokers.

RESULTS

EFFICACY

Table 3: Number (%) of Patients with Key Typical Pathogens Associated with CAP at Screening from Sputum, Respiratory Sample or Blood (Bacteriology ITT and Bacteriology PP Test of Cure Populations)

Pre-Therapy Pathogen	Augmentin XR 2000/125mg bid			
	Bacteriology ITT Population N=142		Bacteriology PP Test of Cure Population N=119	
	n	(%)	n	(%)
<i>S. pneumoniae</i>	58	(40.8)	52	(43.7)
<i>H. influenzae</i>	48	(33.8)	39	(32.8)
<i>Haemophilus parainfluenzae</i>	20	(14.1)	14	(11.8)
MSSA*	12	(8.5)	12	(10.1)
<i>Klebsiella pneumoniae</i>	9	(6.3)	7	(5.9)
<i>M. catarrhalis</i>	6	(4.2)	5	(4.2)

Note: Sponsor's Table: Some patients may have had more than one pathogen

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

Table 4: Per Patient Bacteriological Response at Test of Cure (Bacteriology ITT and Bacteriology PP Test of Cure Populations)

Bacteriological Response	Augmentin XR 2000/125mg bid	
	N=142	
Bacteriology ITT Population		
Success n(%)	119	(83.8)
Failure n(%)	23	(16.2)
Known Failure	17	(12.0)
Unable to Determine*	6	(4.2)
95% CI for success rate	76.5, 89.2	
Bacteriology PP Test of Cure Population		
Success n(%)	105	(88.2)
Failure n(%)	14	(11.8)
95% CI for success rate	80.7, 93.2	

Statistical Reviewer's Comments:

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

Table 5: Clinical Response at Test of Cure (ITT and Clinical PP Test of Cure Populations)

Clinical Response	Augmentin XR 2000/125mg bid	
ITT Population	N=420	
Success n (%)	347	(82.6)
Failure* n (%)	73	(17.4)
95% CI for success rate	78.6, 86.1	
Clinical PP Test of Cure Population	N=333	
Success n (%)	297	(89.2)
Failure n (%)	36	(10.8)
95% CI for success rate	85.2, 92.2	

Statistical Reviewer's Comments:

In the ITT population, the clinical success rate at test of cure was 82.6%. In the Clinical PP test of cure population, the clinical success rate at test of cure was 89.2%.

SAFETY

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

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Adverse Experiences by Relationship to Study Medication

Table 6: Number (%) of Patients with the Most Frequently Reported Adverse Experiences with a Suspected or Probable Relationship to Study Medication ($\geq 1\%$ of Patients)

	Augmentin XR 2000/125mg bid N=420	
	n	(%)
Patients with at Least One AE with Suspected or Probable Relationship	117	(27.9)
Diarrhoea	76	(18.1)
Nausea	13	(3.1)
Abdominal Pain	9	(2.1)
Vomiting	7	(1.7)
Gastritis	5	(1.2)
Headache	4	(1.0)
Moniliasis	4	(1.0)
Moniliasis Genital	4	(1.0)
Thrombocytopenia	4	(1.0)

Statistical Reviewer's Comments:

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

Deaths

According to the sponsor, the deaths of 8 patients were reported during the interval on-therapy and within 30 days post-therapy. In addition, one patient died after completion of the study and more than 30 days post-therapy. All the adverse experiences resulting in death were reported as unrelated or unlikely to be related to study treatment (Table 7).

Table 7: Details of Death

Patient number	Cause of death	Relationship to study medication
547.010.08394	Congestive heart disease	Unrelated
547.010.08395	Pulmonary thromboembolism	Unrelated
547.010.08400	Congestive heart failure	Unrelated
547.083.06417	Acute heart failure	Unrelated
547.117.06322	Possible myocardial infarction	Unrelated
547.173.06897	Lung congestion	Unrelated
547.175.06362	Pulmonary embolism	Unlikely
547.191.06385*	Bronchial neoplasm	Unrelated
547.231.08840	Cardiopulmonary arrest	Unrelated

Sponsor's Table (edited)

* Patient died more than 30 days post-therapy

CONCLUSIONS:**Interim Analysis Review:**

This open, non-comparative, multicentre study was designed to assess the bacteriological and clinical efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days in the treatment of patients with community acquired pneumonia. The primary endpoint of the study was the bacteriological response rate (success/failure) at test of cure (Day 16-37).

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

The primary efficacy variable for this study was bacteriological response (success/failure) at test of cure (bacteriological success was defined as all initial pathogens eradicated or presumed eradicated at the test of cure visit, without any new infection, but with or without colonisation). The success rate at the test of cure visit in the Bacteriology ITT population was 119/142 (83.8%) and in the Bacteriology PP population was 105/119(88.2%). In the ITT population, the clinical success rate at test of cure was 82.6%. In the Clinical PP test of cure population, the clinical success rate at test of cure was 89.2%. It should be noted that this is an open label, non-comparative trial and drawing any meaningful conclusion of efficacy based on the interim analysis results could be misleading.

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

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

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III.

In support of this indication, the sponsor has submitted results from two phase III trials. The study titles and objectives of the two trials are as follows.

Study BRL-025000/548: A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin XR 2000/125mg Twice Daily for 7 Days Versus Oral Clarithromycin 500mg Twice Daily for 7 Days in the Treatment of _____

Study BRL-025000/549: A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin® XR 2000/125mg Twice Daily for 7 Days Versus Oral Levofloxacin 500mg Once a Day for 7 Days in the Treatment of _____

Number of Patients(%) Enrolled* by Drs. DeAbate and Mathew (Excluded Investigators)

Study	Dr. DeAbate	Dr. Mathew	Total
025000/548	0/634	46/634 (7.3%)	46/634 (7.3%)
025000/549	49/673 (7.3%)	0/673	49/673 (7.3%)

Includes all the patients enrolled, whether or not they took study medication.

Based on DSI investigations, the sites of Drs. DeAbate and Mathew were excluded from the efficacy and safety analysis of this NDA submission. A re-analysis of the data was submitted by the sponsor and the results were used for evaluation.

STUDY BRL-025000/548

INTRODUCTION

Study Objectives

Primary: To demonstrate that oral Augmentin XR 2000/125mg twice daily for 7 days was at least as effective clinically as oral clarithromycin 500mg twice daily for 7 days for the treatment of _____

Secondary: To evaluate the bacteriological efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days compared with oral clarithromycin 500mg twice daily for 7 days in patients with _____

METHODOLOGY

Study Design

This was a randomized, double-blind, double-dummy, multicenter, parallel group Phase III study clinical and bacteriological efficacy and the safety of oral Augmentin XR 2000/125mg twice daily comparison to oral clarithromycin 500mg twice daily for 7 days for the treatment of _____

Patients were expected to attend the clinic five times over a duration of approximately five weeks: at screening (Visit 1, Day 0), on-therapy (Visit 2, Day 3-5), end of therapy (Visit 3, Day 9-11), test of cure (Visit 4, Day 14-21) and long-term follow-up (Visit 5, Day 28-35).

Study Population

The study was designed to enroll patients of either gender, at least 40 years of age, with a history of _____ characterized by cough and sputum production for more than two consecutive years and for most days in a consecutive three-month period in each year. Patients were to have _____ characterized by increased purulent sputum together with increased cough and increased dyspnea and be suitable for oral therapy.

Patients were randomly assigned, in equal proportions (1:1) and in a double-blind fashion to receive oral Augmentin XR 2000/125mg twice daily for 7 days or oral clarithromycin 500mg twice daily for 7 days. The batch numbers for study medication were: Augmentin XR B99012 and B99015; Augmentin XR-placebo B99013; clarithromycin U99115; clarithromycin-placebo N99040.

Primary Efficacy Variable

The primary efficacy variable was clinical response (success or failure) at test of cure (Visit 4).

Secondary Efficacy Variables

The secondary efficacy variables were as follows:

- Clinical response (success or failure) at end of therapy (Visit 3).
- Clinical response (success or failure) at long-term follow-up (Visit 5).
- Bacteriological response (success or failure) at test of cure (Visit 4).
- Bacteriological response (success or failure) at end of therapy (Visit 3).
- Bacteriological response (success or failure) at long-term follow-up (Visit 5).

Statistical Reviewer's Comments:

The principal efficacy analysis was based on a comparison of proportions between the treatment groups for the PP and Bacteriology ITT population. Two-sided 95% CIs were used to estimate the difference in the proportion of successes between the treatment groups. A conclusion of non-inferior efficacy of Augmentin XR was drawn if the lower limit of the CI (Augmentin XR minus clarithromycin) was greater than -10%. The robustness of the principal analysis was assessed using PP and ITT and/or Bacteriology ITT populations.

All patients meeting the study entry criteria were randomly assigned, in equal proportions (1:1), and in a double-blind, double-dummy fashion, to receive coded medications according to a pre-determined randomization schedule provided by SB.

Patient Disposition

The numbers of patients who were randomized, received study medication and completed the study, together with the numbers of patients eligible for the various ITT and PP populations, are tabulated by treatment group in Table 1.

Table 1: Patient Disposition (All Randomized Patients)

Population	Treatment Group	
	Augmentin XR 2000/125mg bid	Clarithromycin 500mg bid
	n	n
Randomized	314	320
Received Study Medication (ITT/Safety)*	313	318
Completed Study	274	285
Clinical PP End of Therapy	253	267
Clinical PP Test of Cure	241	260
Clinical PP Long-Term Follow-Up	235	251
Bacteriology ITT	72	69
Bacteriology PP End of Therapy	61	58
Bacteriology PP Test of Cure	52	56
Bacteriology PP Long-Term Follow-Up	49	51

Sponsor's Table

* To be included in the ITT population a patient had to have been randomized and must have taken at least one dose of study medication. A patient was considered to have taken study medication if they had a start date on the compliance page of the CRF and/or the number of tablets recorded as 'taken' on this same page was >0.

Note: This table includes patients evaluated by all the investigators.

A total of 634 patients (Augmentin XR: 314 patients, clarithromycin: 320 patients) were randomized to receive study medication. The numbers of patients who were randomized (and received at least one dose of study medication; ie the ITT/Safety population) and completed the study, by country for the ITT population, are shown in Table 2.

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

Country	Treatment Group			
	Augmentin XR 2000/125mg bid N=313		Clarithromycin 500mg bid N=318	
	R	C	R	C
Mexico	1	0	1	0
US	312	274	317	285
Total	313	274	318	285

R = randomized; C = completed

Demographic and Baseline Characteristics

The Demographic Characteristics for the ITT population is given in Table 3.

Table 3: Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group	
	Augmentin XR 2000/125mg bid N=313	Clarithromycin 500mg bid N=318
Gender, n (%)		
Male	132 (42.2)	147 (46.2)
Female	181 (57.8)	171 (53.8)
Age (yr)		
Mean (SD)	56.3 (12.1)	55.9 (12.0)
Range	38-86	39-91
Race, n (%)		
White	260 (83.1)	273 (85.8)
Black	41 (13.1)	37 (11.6)
Oriental	1 (0.3)	0
Other*	11 (3.5)	8 (2.5)
Weight (kg)**		
Mean (SD)	85.2 (24.8)	84.6 (21.8)
Range	42.0-240.0	41.7-158.6
Height (cm)		
Mean (SD)	169.4 (10.3)	169.4 (10.9)
Range	142.3-205.7	107.2-210.8

* For the Augmentin XR group, the 'Other' races, as recorded by the investigator, were Hispanic (8 patients), Italian-American (one patient), Guyana-Indian (one patient), and Middle Eastern (one patient). For the clarithromycin group, the 'Other' races, as recorded by the investigator, were Hispanic (7 patients) and Native American/German (one patient).

** n = 312 patients for the Augmentin XR group (weight missing for one patient)

Statistical Reviewer's Comments:

In the ITT test of cure population, although no significant difference observed, there was a slightly higher proportion of females than males in both treatment groups. The majority of patients were white. In the ITT population, the mean age was 56.3 years in the Augmentin XR group and 55.9 years in the clarithromycin group. No major differences were evident between the treatment groups in the ITT population.

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Table 4: Clinical and Smoking History (ITT Population)

Characteristic	Treatment Group	
	Augmentin XR 2000/125mg bid N=313	Clarithromycin 500mg bid N=318
Duration of (Years)		
Mean (SD)	12.4 (11.7)	13.6 (11.7)
Range	1.4 - 68.1	2.0 - 54.3
Baseline FEV₁ (% Predicted), n (%)*		
<50%	59 (18.8)	60 (18.9)
50%-70%	72 (23.0)	72 (22.6)
>70%	132 (42.2)	142 (44.7)
Unknown	50 (16.0)	44 (13.8)
Number of Exacerbations Treated with Antibacterials in Last Year, n (%)		
0	59 (18.8)	58 (18.2)
1-4	228 (72.8)	237 (74.5)
>4	26 (8.3)	23 (7.2)
Use of Supplemental Oxygen, n (%)		
Yes	12 (3.8)	13 (4.1)
Use of Systemic Corticosteroids in Last Year, n (%)**		
Yes	50 (16.0)	60 (18.9)
Smoking History, n (%)		
Current Smoker	145 (46.3)	148 (46.5)
Previous Smoker	243 (77.6)	235 (73.9)
Smoking Pack Years:		
0	68 (21.7)	79 (24.8)
>0-10	54 (17.3)	44 (13.8)
>10-20	52 (16.6)	34 (10.7)
>20-30	37 (11.8)	40 (12.6)
>30	102 (32.6)	119 (37.4)
Unknown	0	2 (0.6)
Inpatient, n (%) †		
Yes	0	0

Sponsor's Table -

* If a patient had an FEV₁ measurement taken on or between 6 days and 12 months prior to screening, the percent predicted FEV₁ was derived from this historical measurement as described in reference [14]; otherwise this value was derived from a measurement taken at or between end of therapy and long-term follow-up. The FEV₁ measurement was not to be taken during an exacerbation.

** Used for pulmonary disease.

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Statistical Reviewer's Comments:

In the ITT population, there was a slightly greater proportion of patients with a smoking history of >30 pack years in the clarithromycin group (37.4% of patients) than in the Augmentin XR group (32.6% of patients). The mean duration of _____ was approximately 12 years in the Augmentin XR group and 14 years in the clarithromycin group. In addition, 8.3% of patients in the Augmentin XR group and 7.2% of patients in the clarithromycin group had experienced more than four exacerbations of _____ in the last year that required treatment with antibacterials.

Table 5: Clinical Evaluation of Current Episode of _____ at Screening (ITT Population)

Characteristic	Treatment Group	
	Augmentin XR 2000/125mg bid N=313	Clarithromycin 500mg bid N=318
Auscultatory Findings, n (%)		
Wheeze	141 (45.0)	159 (50.0)
Rales	119 (38.0)	115 (36.2)
Crackles	120 (38.3)	124 (39.0)
Sputum Characteristics, n (%)		
Increased Volume of Purulent Sputum	313 (100.0)	318 (100.0)
Increased Sputum Purulence	297 (94.9)	300 (94.3)
Increased Cough, n (%)		
Yes	313 (100.0)	318 (100.0)
Mild	25 (8.0)	31 (9.7)
Moderate	187 (59.7)	188 (59.1)
Severe	101 (32.3)	99 (31.1)
Increased Dyspnea, n (%)		
Yes	313 (100.0)	318 (100.0)
Mild	84 (26.8)	80 (25.2)
Moderate	173 (55.3)	182 (57.2)
Severe	56 (17.9)	56 (17.6)
Duration of Current Exacerbation (Days)		
Mean (SD)	14 (14.9)	11.8 (11.4)
Range	1 - 90	1 - 90
Peak Flow at Screening (% predicted)*		
Number of Patients Assessed	313	312
Mean (SD)	60.4 (22.8)	59.7 (22.7)

Sponsor's Table

* Peak flow = peak expiratory flow rate (PEFR), calculated as described in reference [15] in sponsor's report.

Statistical Reviewer's Comments:

At screening, in the ITT population with respect to the clinical evaluation of the current episode of — the proportion of clarithromycin-treated patients who had an auscultatory finding of wheeze was slightly greater than the proportion of Augmentin XR-treated patients with wheeze. In the ITT population at screening, more than 90% of patients in each treatment group had cough of at least moderate severity and more than 73% of patients in each treatment group had dyspnea of at least moderate severity.

RESULTS**EFFICACY**

Table 6 : Clinical Response at Test of Cure (Clinical PP Test of Cure and ITT Populations)- Reanalysis Results (Excluding the investigators listed above)

Clinical Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Clarithromycin 500 mg bid
Clinical PP Test of Cure Population	N=221	N=240
Success n (%)	187 (84.6)	206 (85.8)
Failure n (%)	34 (15.4)	34 (14.2)
Clinical Failure at End of Therapy	21 (9.5)	21 (8.8)
Clinical Recurrence at Test of Cure	13 (5.9)	13 (5.4)
95% CI	(-7.7, 5.3)	
ITT Population	N=290	N=295
Success n (%)	229 (79.0)	240 (81.4)
Failure n (%)	61 (21.0)	55 (18.6)
Clinical Failure at End of Therapy	27 (9.3)	12 (6.9)
Clinical Recurrence at Test of Cure	14 (4.8)	0
Unable to Determine	20 (6.9)	13 (7.4)
95% CI	(-8.9, 4.1)	

Statistical Reviewer's Comments:

In the Clinical PP test of cure population, the clinical success rates at test of cure were 84.6% in the Augmentin XR group and 85.8% in the clarithromycin group. In the ITT population, the clinical success rates at test of cure were 79.0% in the Augmentin XR group and 81.4% in the clarithromycin group. The clinical equivalence of Augmentin XR was shown to be at least as good as that of clarithromycin, as the lower limit of the 95% CI (-8.9, 4.1) for the treatment difference was no less than the non-inferiority margin of -10%.

Table 7: Bacteriological Response at Test of Cure (Bacteriological PP and ITT Populations)- Reanalysis Results (Excluding the investigators)

Bacteriological Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Clarithromycin 500 mg bid
Bacteriological PP Test of Cure Population	N=40	N=41
Success n (%)	30 (75.0)	32 (78.0)
Failure n (%)	10 (25.0)	9 (22.0)
95% CI	(-21.5, 15.4)	
Bacteriological ITT Population	N=56	N=52
Success n (%)	36 (64.3)	37 (71.2)
Failure n (%)	20 (35.7)	15 (28.8)
95% CI	(-24.5, 10.7)	

Statistical Reviewer's Comments:

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

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Table 8: Initial Pathogen Bacteriological Outcome at Test of Cure (For All Pathogens Combined and Key Pathogens) (Bacteriology PP Test of Cure Population)

Initial Pathogen	Bacteriological Outcome	Treatment Group			
		Augmentin XR 2000/125mg bid N=52		Clarithromycin 500mg bid N=56	
		n	(%)	n	(%)
All Pathogens	<i>n</i>	70		71	
	Eradication	3	(4.3)	3	(4.2)
	Presumed Eradication	52	(74.3)	50	(70.4)
	Failure	8	(11.4)	5	(7.0)
	Presumed Failure	2	(2.9)	12	(16.9)
	Unable to Determine*	5	(7.1)	1	(1.4)
<i>H. influenzae</i>	<i>n</i>	17		10	
	Presumed Eradication	13	(76.5)	7	(70.0)
	Failure	3	(17.6)	1	(10.0)
	Presumed Failure	1	(5.9)	2	(20.0)
MSSA	<i>n</i>	8		10	
	Presumed Eradication	7	(87.5)	6	(60.0)
	Failure	0		2	(20.0)
	Presumed Failure	1	(12.5)	1	(10.0)
	Unable to Determine*	0	(0)	1	(10.0)
<i>H. parainfluenzae</i>	<i>n</i>	9		16	
	Eradication	1	(11.1)	1	(6.3)
	Presumed Eradication	5	(55.6)	15	(93.8)
	Failure	2	(22.2)	0	
	Unable to Determine*	1	(11.1)	0	
<i>M. catarrhalis</i>	<i>n</i>	9		12	
	Eradication	1	(11.1)	2	(16.7)
	Presumed Eradication	7	(77.8)	8	(66.7)
	Presumed Failure	0		2	(16.7)
	Unable to Determine*	1	(11.1)	0	
<i>S. pneumoniae</i>	<i>n</i>	5		9	
	Eradication	1	(20.0)	0	
	Presumed Eradication	3	(60.0)	6	(66.7)
	Presumed Failure	0		3	(33.3)
	Unable to Determine*	1	(20.0)	0	

Sponsor's Table

* Augmentin XR-treated patients 548.130.07411, 548.130.07413, and 548.205.10542 and clarithromycin-treated patient 548.120.07457 were all Clinical PP failures at end of therapy and, hence, were into the Bacteriology PP test of cure population, with an outcome of 'unable to determine' for pathogens in the Augmentin XR group and the one eradicated pathogen in the clarithromycin group.

Note: n (%) = number (%) of pathogens with a particular outcome; n = total number of pathogens.

The failure category includes pathogens which persisted at end of therapy or recurred at test of cure. The presumed failure category includes pathogens which were presumed to have persisted at end of therapy or presumed to have recurred at test of cure. The 'unable to determine' category includes pathogens which were eradicated or presumed eradicated at end of therapy in patients who were clinical failures at end of therapy.

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Statistical Reviewer's Comments:

In the Bacteriology PP test of cure population, the majority of initial pathogens were either eradicated or presumed eradicated at test of cure (Augmentin XR: 55/70 isolates, 78.6%; clarithromycin: 53/71 isolates, 74.6%). Small number of isolates were identified/reported for individual pathogens as given in Table 8.

SAFETY

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

Adverse Experiences

The numbers of patients with the most frequently reported AEs, by preferred term, are summarized in Table 9.

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

Preferred Term	Treatment Group			
	Augmentin XR 2000/125mg bid N=313		Clarithromycin 500mg bid N=318	
	n	(%)	n	(%)
Patients with at Least One AE	197	(62.9)	199	(62.6)
Diarrhea	83	(26.5)	34	(10.7)
Headache	21	(6.7)	15	(4.7)
Nausea	19	(6.1)	21	(6.6)
Moniliasis Genital	16	(5.1)	2	(0.6)
Infection Viral	12	(3.8)	5	(1.6)
Upper Respiratory Tract Infection	11	(3.5)	3	(0.9)
Rhinitis	10	(3.2)	14	(4.4)
Abdominal Pain	9	(2.9)	17	(5.3)
Infection Fungal	9	(2.9)	1	(0.3)
Injury	9	(2.9)	7	(2.2)
Vomiting	8	(2.6)	8	(2.5)
Sinusitis	7	(2.2)	13	(4.1)
Taste Perversion	3	(1.0)	34	(10.7)
Flatulence	3	(1.0)	11	(3.5)
Pharyngitis	5	(1.6)	10	(3.1)
Constipation	5	(1.6)	7	(2.2)
Myalgia	5	(1.6)	7	(2.2)
Insomnia	4	(1.3)	7	(2.2)
Mouth Dry	4	(1.3)	7	(2.2)

Sponsor's Table

Statistical Reviewer's Comments:

According to the sponsor, during the interval on-therapy plus 30 days post-therapy, at least one AE was reported by 62.9% of patients in the Augmentin XR group and 62.6% of patients in the clarithromycin group. The most frequently reported adverse experience in the Augmentin XR

group was diarrhea (26.5%). In the clarithromycin group, the most frequently reported AEs were diarrhea (10.7%) and taste perversion (10.7%).

Adverse Experiences by Relationship to Study Medication

The numbers (%) of patients with the most frequently reported suspected or probably related AEs (including AEs of unknown causality) are summarized in Table 10.

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

Preferred Term	Treatment Group			
	Augmentin XR 2000/125mg bid N=313		Clarithromycin 500mg bid N=318	
	n	(%)	n	(%)
Patients with at Least One AE of Suspected or Probable Relationship	123	(39.3)	101	(31.8)
Diarrhea	74	(23.6)	30	(9.4)
Moniliasis Genital	15	(4.8)	2	(0.6)
Nausea	13	(4.2)	18	(5.7)
Infection Fungal	9	(2.9)	1	(0.3)
Abdominal Pain	5	(1.6)	13	(4.1)
Gastrointestinal Disorder NOS	4	(1.3)	1	(0.3)
Moniliasis	4	(1.3)	1	(0.3)
Flatulence	3	(1.0)	9	(2.8)
Headache	3	(1.0)	1	(0.3)
Mouth Dry	3	(1.0)	1	(0.3)
Taste Perversion	3	(1.0)	32	(10.1)
Vomiting	3	(1.0)	4	(1.3)
Dyspepsia	0		5	(1.6)

Sponsor's Table

Note: AEs of "Unknown" causality are also included

Statistical Reviewer's Comments:

In the Augmentin XR group, during the interval on-therapy plus 30 days post-therapy, 39.3% of patients and 31.8% of patients in the clarithromycin group reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication.

Noticeably, a higher proportion of patients in the Augmentin XR group (23.6%) reported diarrhea that was considered to be of suspected or probable relationship to study medication compared to the proportion of patients in the clarithromycin group (9.4%). In addition, 4.8% of Augmentin XR-treated patients reported genital moniliasis that was considered to be of suspected or probable relationship to study medication compared to 0.6% of clarithromycin-treated patients. In the clarithromycin group, 10.1% of patients reported taste perversion as being of suspected or probable relationship to study medication compared to 1.0% of patients in the Augmentin XR group.

CONCLUSIONS:

STUDY BRL-025000/548 is a randomized, double-blind, double-dummy, multicenter, parallel group study, designed to assess the clinical and bacteriological 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 patients with _____

In the Clinical PP test of cure population, the clinical success rates at test of cure were 84.6% in the Augmentin XR group and 85.8% in the clarithromycin group. In the ITT population, the clinical success rates at test of cure were 79.0% in the Augmentin XR group and 81.4% in the clarithromycin group. The clinical equivalence of Augmentin XR was shown to be at least as good as that of clarithromycin, as the lower limit of the 95% CI (-8.9, 4.1) for the treatment difference was no less than the non-inferiority margin of -10%.

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

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

In this study, the role of *streptococcus pneumoniae* with reduced susceptibility to penicillin in _____ is unclear.

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STUDY BRL-025000/549

INTRODUCTION

Study Objectives

Primary: To demonstrate that oral Augmentin XR 2000/125mg twice daily for 7 days was at least as effective clinically as oral levofloxacin 500mg once daily for 7 days for the treatment of

Secondary: To evaluate the bacteriological efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days compared with oral levofloxacin 500mg once daily for 7 days in patients with

METHODOLOGY

Study Design

This was a randomised, double-blind, double-dummy, multicentre, parallel group, Phase III study to assess the clinical and bacteriological efficacy and the safety of oral Augmentin XR 2000/125mg twice daily in comparison to oral levofloxacin 500mg once daily for 7 days for the treatment of

Patients were expected to attend the clinic five times over a duration of approximately five weeks: at screening (Visit 1, Day 0), on-therapy (Visit 2, Day 3-5), end of therapy (Visit 3, Day 9-11), test of cure (Visit 4, Day 14-21) and long-term follow-up (Visit 5, Day 28-35).

The study was conducted at a total of 93 centres in 6 countries. The participating countries (number of centres) were Belgium (7 centres), France (22 centres), Germany (20 centres), Ireland (8 centres), United Kingdom (11 centres) and the USA (25 centres).

Primary Efficacy Variable

The primary efficacy variable was clinical response (success or failure) at test of cure (Visit 4).

Secondary Efficacy Variables

Clinical response (success or failure) at end of therapy (Visit 3).

Clinical response (success or failure) at long-term follow-up (Visit 5).

Bacteriological response (success or failure) at test of cure (Visit 4).

Bacteriological response (success or failure) at end of therapy (Visit 3).

Bacteriological response (success or failure) at long-term follow-up (Visit 5).

Statistical Reviewer's Comments:

The principal efficacy analysis was based on a comparison of proportions between the treatment groups for the PP and ITT and/or Bacteriological ITT populations. Two-sided 95% CIs were used to estimate the difference in the proportion of successes between the treatment groups. A conclusion of non-inferior efficacy of Augmentin XR was drawn if the lower limit of the

CI (Augmentin XR minus levofloxacin) was > -10%. The robustness of the principal analysis was assessed using PP and ITT and/or Bacteriology ITT populations.

Patient Disposition

The numbers of patients who were randomised, received study medication and completed the study, together with the numbers of patients eligible for the various ITT and PP populations, are tabulated by treatment group in Table 1.

Table 1: Patient Disposition (All Randomised Patients)

Population	Treatment Group	
	Augmentin XR 2000/125mg bid	Levofloxacin 500mg od
	n	n
Randomised	332	341
Received Study Medication (ITT/Safety)	331	340
Completed Study	294	302
Clinical PP End of Therapy	279	290
Clinical PP Test of Cure	275	283
Clinical PP Long-Term Follow-Up	264	277
Bacteriology ITT	96	96
Bacteriology PP End of Therapy	83	82
Bacteriology PP Test of Cure	80	74
Bacteriology PP Long-Term Follow-Up	78	73

Sponsor's Table

Note: This table includes patients evaluated by all the investigators.

Statistical Reviewer's Comments:

A total of 673 patients (Augmentin XR: 332 patients, levofloxacin: 341 patients) were randomised to receive study medication. One patient in each group (Augmentin XR: 549.172.04062, levofloxacin: 549.105.03987) was withdrawn from the study before the first dose of study medication had been administered. The 671 patients who received at least one dose of study medication comprised the ITT population.

Demographic Characteristics

Demographic characteristics for the ITT population is presented in Table 2.

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Table 2: Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group	
	Augmentin XR 2000/125mg bid N=331	Levofloxacin 500mg od N=340
Gender, n (%)		
Male	200 (60.4)	192 (56.5)
Female	131 (39.6)	148 (43.5)
Age (yr)		
Mean (SD)	61.5 (12.1)	60.4 (12.0)
Range	39 - 91	37 - 92
Race, n (%)		
White	300 (90.6)	308 (90.6)
Black	26 (7.9)	26 (7.6)
Oriental	1 (0.3)	2 (0.6)
Other*	4 (1.2)	4 (1.2)
Weight (kg)**		
Mean (SD)	77.4 (19.2)	76.4 (17.6)
Range	33.0 - 167.7	40.0 - 165.0
Height (cm)†		
Mean (SD)	168.3 (9.3)	168.0 (10.2)
Range	142.2 - 193.0	143.0 - 190.5

* The other races, as recorded verbatim by the investigator, were North African (2 patients), Hispanic (2 patients) and Arab, Spanish, half-caste and Indian/Asian (1 patient each).

** n = 339 for levofloxacin group (weight missing for one patient).

† n = 330 for Augmentin XR group, n=339 for levofloxacin group (height missing for one patient in each group).

Statistical Reviewer's Comments:

In the ITT population at test of cure, the two treatment groups were not very different with respect to demographic characteristics and no major differences were evident. Patients with _____ the study population was predominantly elderly. For the ITT population, the mean age was 61.5 years in the Augmentin XR group and 60.4 years in the levofloxacin group. In both the treatment groups there were more males than females and the majority of patients were white.

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RESULTS

EFFICACY

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

Table 3: Clinical Response at Test of Cure (Clinical PP Test of Cure and ITT Populations)- Reanalysis Results (Excluding the investigators)

Clinical Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Levofloxacin 500mg od
Clinical PP Test of Cure Population	N=255	N=264
Success n (%)	219 (85.9)	230 (87.1)
Failure n (%)	36 (14.1)	34 (12.9)
Clinical Failure at End of Therapy	14 (5.5)	18 (6.8)
Clinical Recurrence at Test of Cure	22 (8.6)	16 (6.1)
95% CI	(-7.7, 4.6)	
ITT Population	N=307	N=315
Success n (%)	245 (79.8)	254 (80.6)
Failure n (%)	62 (20.2)	61 (19.4)
Clinical Failure at End of Therapy	17 (5.5)	23 (7.3)
Clinical Recurrence at Test of Cure	22 (7.2)	17 (5.4)
Unable to Determine	23 (7.5)	21 (6.7)
95% CI	(-7.1, 5.4)	

Statistical Reviewer's Comments:

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

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Table 4: Bacteriological Response at Test of Cure (Bacteriological PP and ITT Populations)- Reanalysis Results (Excluding the investigators)

Bacteriological Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Levofloxacin 500mg od
Bacteriological PP Test of Cure Population	N=65	N=59
Success n (%)	52 (80.0)	49 (83.1)
Failure n (%)	13 (20.0)	10 (16.9)
95% CI	(-16.7, 10.6)	
Bacteriological ITT Population	N=78	N=75
Success n (%)	59 (75.6)	55 (73.3)
Failure n (%)	19 (24.4)	20 (26.7)
95% CI	(-11.5, 16.1)	

Statistical Reviewer's Comments:

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

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Table 5: Initial Pathogen Bacteriological Outcome at Test of Cure (For All Pathogens Combined and Key Pathogens) (Bacteriology PP Test of Cure Population)

Initial Pathogen	Bacteriological Outcome	Treatment Group			
		Augmentin XR 2000/125mg bid N=80		Levofloxacin 500mg od N=74	
	<i>n</i>	<i>n</i>	(%)	<i>n</i>	(%)
All Pathogens	<i>n</i>	103		93	
	Eradication	14	(13.6)	7	(7.5)
	Presumed Eradication	70	(68.0)	72	(77.4)
	Failure	12	(11.7)	5	(5.4)
	Presumed Failure	5	(4.9)	9	(9.7)
	Unable to Determine	2*	(1.9)	0	
<i>H. influenzae</i>	<i>n</i>	27		24	
	Eradication	2	(7.4)	3	(12.5)
	Presumed Eradication	20	(74.1)	20	(83.3)
	Failure	4	(14.8)	0	
	Presumed Failure	1	(3.7)	1	(4.2)
<i>H. parainfluenzae</i>	<i>n</i>	20		17	
	Eradication	2	(10.0)	1	(5.9)
	Presumed Eradication	12	(60.0)	14	(82.4)
	Failure	4	(20.0)	0	
	Presumed Failure	1	(5.0)	2	(11.8)
	Unable to Determine	1*	(5.0)	0	
<i>S. pneumoniae</i>	<i>n</i>	15		8	
	Eradication	0		2	(25.0)
	Presumed Eradication	14	(93.3)	6	(75.0)
	Unable to Determine	1*	(6.7)	0	
<i>M. catarrhalis</i>	<i>n</i>	14		12	
	Eradication	4	(28.6)	0	
	Presumed Eradication	7	(50.0)	12	(100.0)
	Presumed Failure	3	(21.4)	0	
MSSA	<i>n</i>	9		10	
	Eradication	2	(22.2)	1	(10.0)
	Presumed Eradication	7	(77.8)	7	(70.0)
	Failure	0		1	(10.0)
	Presumed Failure	0		1	(10.0)

Sponsor Table

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

* Patient 549.503.08265 had two initial pathogens at screening, *H. parainfluenzae* and *S. pneumoniae*. Both of these pathogens were eradicated at the end of therapy, but the patient had a superinfection with *M. catarrhalis* and so was included in the PP population at the end of therapy as a bacteriological failure. Failures are carried forward, therefore the patient was included in the PP population at test of cure, with an outcome of unable to determine for the two eradicated pathogens.

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

Statistical Reviewer's Comments:

In the Bacteriology PP test of cure population, the majority of initial isolates were either eradicated or presumed eradicated at test of cure (Augmentin XR: 84/103 isolates, 81.6%; levofloxacin: 79/93 isolates, 84.9%). Individual pathogens (*H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, *M. catarrhalis* and *MSSA*) were reported to have smaller number of isolates.

SAFETY

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

Adverse Experiences by Relationship to Study Medication

During the interval on-therapy plus 30 days post-therapy, 19.6% of patients in the Augmentin XR group and 17.1% of patients in the levofloxacin group reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication (including AEs of unknown causality). The number (%) of patients with the most frequently reported suspected or probably related AEs are summarised in Table 6.

Table 6: Number (%) of Patients with the Most Frequently Reported Adverse Experiences with a Suspected or Probable Relationship to Study Medication (≥1% of Patients)

Preferred Term	Treatment Group			
	Augmentin XR 2000/125mg bid N=331		Levofloxacin 500mg od N=340	
	n	(%)	n	(%)
Patients with at Least One AE of Suspected or Probable Relationship	65	(19.6)	58	(17.1)
Diarrhoea	39	(11.8)	12	(3.5)
Nausea	9	(2.7)	12	(3.5)
Moniliasis	5	(1.5)	2	(0.6)
Abdominal Pain	3	(0.9)	5	(1.5)
Dizziness	2	(0.6)	4	(1.2)

Sponsor's Table

Note: AEs of unknown causality are also included.

Statistical Reviewer's Comments:

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

CONCLUSIONS

This randomised, double-blind, double-dummy, multicentre, parallel group study was designed to assess the clinical and bacteriological 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 patients with _____ The primary endpoint of the study was the clinical response rate (success/failure) at test of cure (Day 14-23).

The primary efficacy variable for this study was clinical response (success/ failure) at test of cure (clinical success was defined as the sufficient resolution of the signs and symptoms of _____ such that no additional antibacterial therapy was indicated for _____)

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

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

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

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

In this study, the role of *streptococcus pneumoniae* with reduced susceptibility to penicillin in _____ is unclear.

IV. ACUTE BACTERIAL SINUSITIS (ABS)

In support of this indication, the sponsor has submitted results from two phase III trials. The study titles and objectives of the two trials are as follows.

Study BRL-025000/550: A Randomized, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin® XR, Two Tablets Equal to 2000/125mg, Twice Daily for 10 Days Versus Levofloxacin (Levaquin®) 500mg Once Daily for 10 Days in the Treatment of Adults with Acute Bacterial Sinusitis Infections.

Study BRL-025000/551: An Open, Non-Comparative Multicentre Study to Assess the Efficacy and Safety of Oral Augmentin XR 2000/125mg Twice Daily for 10 Days in the Treatment of Acute Bacterial Sinusitis in Adults.

Number of Patients(%) Enrolled* by Drs. DeAbate and Dr. Mathew (Excluded Investigators)

Study	Dr. DeAbate	Dr. Mathew	Total
025000/550	39/432 (9.0%)	30/432 (6.9%)	69/432 (16.0%)
025000/551	0/861	55/861 (6.4%)	55/861 (6.4%)

Note: Includes all the patients enrolled, whether or not they took study medication.

Based on DSI investigations, the sites of Drs. DeAbate and Mathew were excluded from the efficacy and safety analysis of this NDA submission. A re-analysis of the data was submitted by the sponsor and those results were used for evaluation.

STUDY BRL-025000/550

INTRODUCTION

Study Objectives

Primary: To demonstrate that the clinical efficacy of Augmentin XR 2000/125mg twice daily for 10 days was at least as effective as that of levofloxacin 500mg once daily for 10 days in the treatment of acute bacterial sinusitis (ABS).

Secondary: To evaluate the bacteriological efficacy and safety of Augmentin XR 2000/125mg twice daily for 10 days compared with levofloxacin 500mg once daily for 10 days in patients with ABS.

METHODOLOGY

Study Design

This was a randomised, multicentre, double-blind, double-dummy, parallel group, Phase III study to assess the clinical and bacteriological efficacy and safety of oral Augmentin XR in

comparison with oral levofloxacin in patients with ABS. All patients meeting the study entry criteria were randomly assigned (1:1 ratio) to receive one of the following coded medications for 10 days: oral Augmentin XR 2000/125mg twice daily (bid) or oral levofloxacin 500mg once daily (od).

Study Population

The study was designed to enrol patients of either gender and at least 18 years of age who presented with signs and symptoms of ABS of at least 7 but less than 28 days duration (defined by purulent nasal discharge or purulence in the nasal cavity and at least one major or two minor specified criteria of ABS). Patients were to have radiological confirmation of ABS.

Primary Efficacy Variable

- The primary efficacy variable was the combined clinical and radiological response (success, failure or unable to determine) at test of cure (Visit 4).

Secondary Efficacy Variables

Clinical response (success or failure) at test of cure (Visit 4)
Clinical response (success or failure) at end of therapy (Visit 3).
Bacteriological response (success or failure) at test of cure (Visit 4).
Bacteriological response (success or failure) at end of therapy (Visit 3).

The increasing evidence of antibacterial resistance in the pathogens commonly associated with ABS has raised concern about the efficacy of currently available therapies and the sponsor's intention was to obtain an approval for the treatment of penicillin resistant pneumococcus (PRSP) in the treatment of acute bacterial sinusitis (ABS).

Statistical Reviewer's Comments:

The principal efficacy analysis was based on a comparison of proportions between the treatment groups for the combined Clinical and Radiological response for PP and ITT/Bacteriology ITT population. Two-sided 95% CIs were used to estimate the difference in the proportion of successes between the treatment groups. A conclusion of non-inferior efficacy of Augmentin XR was drawn if the lower limit of the CI (Augmentin XR minus Levofloxacin) was greater than -10%.

Patient Disposition

The numbers of patients who were randomised to treatment, received study medication (ie the ITT/safety population) and completed the study, and the numbers in each study population are shown in Table 1.

Table 1: Patient Disposition (All Randomised Patients)

Population	Treatment Group	
	Augmentin XR 2000/125mg bid	Levofloxacin 500mg od
	n	n
Randomised	214	218
Received Study Medication (ITT/Safety)	212	216
Completed Study	191	198
Clinical PP End of Therapy	157	169
Clinical PP Test of Cure	150	161
Bacteriology ITT	20	15
Bacteriology PP End of Therapy	15	11
Bacteriology PP Test of Cure	15	10

Sponsor's Table

Note: This table includes patients evaluated by all the investigators.

In total, 432 patients were randomised to study treatments; 214 were randomised to receive Augmentin XR and 218 to receive levofloxacin. According to the sponsor, there were 428 patients in the ITT population since 4 patients (two in each group) were withdrawn before treatment was given. Three of these patients withdrew their consent to participation and the sinus X-ray was normal in the case of the fourth patient.

The numbers of patients in the ITT population who were randomised to treatment and completed treatment, in each country, are shown in Table 2. The study was carried out at 62 centres in France (19 centres), Germany (14 centres) and the USA (29 centres).

Table 2 Number of Patients Who Were Randomised and Completed the Study, by Country (ITT Population)

Country	Treatment Group			
	Augmentin XR 2000/125mg bid N=212		Levofloxacin 500mg od N=216	
	R	C	R	C
France	32	31	30	28
Germany	33	31	30	30
USA	147	129	156	140
Total	212	191	216	198

Sponsor's Table: R = randomised; C = completed

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Demographic Characteristics

The demographic characteristics of patients in the ITT population are shown in Table 3.

Table 3: Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group	
	Augmentin XR 2000/125mg bid N=212	Levofloxacin 500mg od N=216
Gender n (%)		
Male	92 (43.4)	101 (46.8)
Female	120 (56.6)	115 (53.2)
Age (yr)		
Mean (SD)	41.1 (13.2)	39.9 (12.8)
Range	18 – 75	18 – 73
Race n (%)		
White	178 (84.0)	161 (74.5)
Black	27 (12.7)	45 (20.8)
Oriental	2 (0.9)	3 (1.4)
Other*	5 (2.4)	6 (2.8)
Unknown	0	1 (0.5)
Weight (kg)		
Mean (SD)	78.7 (19.1)	82.4 (21.3)
Range	20** – 136.1	47.2 – 181.4
Height*** (cm)		
Mean (SD)	170.7 (10.5)	171.2 (9.6)
Range	138.4 – 210.8	118 – 193

* The other races, as recorded verbatim by the investigator, were Hispanic (9 patients), Asian (one patient) and one patient who refused to state his race.

** The weight of 20kg was recorded incorrectly on the database and upon checking was found to be 70 kg. The minimum weight in the Augmentin XR group was 41.7kg.

*** One patient in the levofloxacin group with data missing for height.

Statistical Reviewer's Comments:

Overall, approximately 55% of patients were female and a majority of patients in each treatment group were white (84.0% in the Augmentin XR group and 74.5% in the levofloxacin group). The mean age of patients was 41.1 years in the Augmentin XR group and 39.9 years in the levofloxacin group. No major differences were evident between the two treatment groups.

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RESULTS

EFFICACY

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

Table 4: Combined Clinical and Radiological Response at Test of Cure (Clinical PP Test of Cure and ITT Populations)- Excluding the Investigators

Combined Clinical and Radiological Response	Treatment Group	
	Augmentin XR 2000/125mg bid	Levofloxacin 500mg od
Clinical PP Test of Cure Population	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)
95% CI	(-9.4, 8.3)	
ITT Population	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)
95% CI	(-14.9, 1.7)	

Statistical Reviewer's Comments:

Excluding the investigators listed above, the combined clinical and radiological response in the Clinical PP test of cure population was 83.7% in the Augmentin XR group and 84.3% in the levofloxacin group. Results in the ITT population were 76.4% in the Augmentin XR group and 83.0% in the levofloxacin group. The combined clinical and radiological response of Augmentin XR was shown to be at least as good as that of levofloxacin in the PP population (95% CI: -9.4, 8.3) and efficacy was not demonstrated in the ITT population (95% CI: -14.9, 1.7) since the lower limit of the 95% CI for the difference in success rates (Augmentin XR – levofloxacin) was less than the tolerable limit (-10%).

Bacteriological Response

The per pathogen bacteriological outcome at test of cure (Day 17-28) for all initial pathogens and the key pathogens associated with ABS is shown in Table 5 for the Bacteriological PP test of cure population.

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Table 5: Initial Pathogen Bacteriological Outcome at Test of Cure (For All Pathogens Combined and Key Pathogens) (Bacteriology PP Test of Cure Population)

Initial Pathogen	Bacteriological Outcome	Treatment Group			
		Augmentin XR		Levofloxacin	
		2000/125mg bid N=15		500mg od N=10	
		n	(%)	n	(%)
All Pathogens	<i>n</i> *	17		11	
	Eradication	0		0	
	Presumed Eradication	15	(88.2)	11	(100.0)
	Failure	0		0	
	Presumed Failure	2	(11.8)	0	
<i>S. pneumoniae</i>	<i>n</i>	7		3	
	Eradication	0		0	
	Presumed Eradication	7	(100.0)	3	(100.0)
	Failure	0		0	
	Presumed Failure	0		0	
<i>H. influenzae</i>	<i>n</i>	3		2	
	Eradication	0		0	
	Presumed Eradication	3	(100.0)	2	(100.0)
	Failure	0		0	
	Presumed Failure	0		0	
MSSA	<i>n</i>	3		1	
	Eradication	0		0	
	Presumed Eradication	3	(100.0)	1	(100.0)
	Failure	0		0	
	Presumed Failure	0		0	
<i>M. catarrhalis</i>	<i>n</i>	1		1	
	Eradication	0		0	
	Presumed Eradication	1	(100.0)	1	(100.0)
	Failure	0		0	
	Presumed Failure	0		0	

Sponsor's Table

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

Note: Patients with bacteriological outcomes in this table are not mutually exclusive.

Statistical Reviewer's Comments:

Based on the above table, the outcome for all the pathogens was presumed eradication in both the treatment groups. Although the isolates were so small, the eradication rates were; Augmentin XR (88.2%) and levofloxacin (100.0%) There were no failures/presumed failures in the levofloxacin group.

SAFETY

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

Adverse Experiences by Relationship to Study Medication

The most commonly reported of these experiences (ie those occurring in at least 1% of patients in either treatment group) are summarised in Table 6.

Table 6: Number (%) of Patients with the Most Frequently Reported Adverse Experiences with a Suspected or Probable Relationship to Study Medication ($\geq 1\%$ of Patients)

Preferred Term	Treatment Group			
	Augmentin XR 2000/125mg bid N=212		Levofloxacin 500mg od N=216	
	n	(%)	n	(%)
Patients with at Least One AE with Suspected or Probable Relationship	80	(37.7)	44	(20.4)
Diarrhoea	51	(24.1)	14	(6.5)
Genital Moniliasis	9	(4.2)	2	(0.9)
Nausea	8	(3.8)	11	(5.1)
Abdominal Pain	5	(2.4)	4	(1.9)
Dyspepsia	5	(2.4)	2	(0.9)
Dry Mouth	0		3	(1.4)

Sponsor's Table

AEs of unknown causality would also be included but none occurred in the study.

Statistical Reviewer's Comments:

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

CONCLUSION

This was a randomised, double-blind, double-dummy, multi-center, parallel group study designed to assess the clinical and bacteriological 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 patients with clinically and radiologically confirmed ABS. The primary endpoint was the combined clinical and radiological response rate (success, failure or unable to determine) at test of cure. Secondary efficacy variables included clinical response rates at the end of therapy and test of cure, and bacteriological response rates at the end of therapy and test of cure in patients at selected centres where sinus endoscopy or rhinoscopy was performed.

The combined clinical and radiological success rate at test of cure (excluding the problematic investigators) in the Clinical PP population was 83.7% in the Augmentin XR group and 84.3% in the levofloxacin group. Results in the ITT population were 76.4% in the Augmentin XR group and 83.0% in the levofloxacin group. The combined clinical and radiological response of Augmentin XR was shown to be at least as good as that of levofloxacin in the PP population (95% CI: -9.4, 8.3). Efficacy was not demonstrated in the ITT population (95% CI: -14.9, 1.7) since the lower limit of the 95% CI for the difference in success rates was less than the tolerable limit (-10%).

Although the approval is sought for the treatment of penicillin resistant pneumococcus (PRSP) in the treatment of acute bacterial sinusitis (ABS), there were no patients with an isolate of PRSP. Hence, this study failed to provide any evidence to support the indication requested.

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

STUDY BRL-025000/551

INTRODUCTION

Study Objectives

Primary: To assess the bacteriological efficacy at the test of cure visit (Days 17-24) of oral Augmentin XR 2000/125mg twice daily (bid) for 10 days in patients with acute bacterial sinusitis (ABS), in particular, infection due to penicillin-resistant *Streptococcus pneumoniae* (PRSP).

Secondary:

To assess the bacteriological and clinical efficacy at the end of therapy visit (Days 12-14) of oral Augmentin XR 2000/125mg bid for 10 days in patients with ABS, in particular, infection due to PRSP.

To evaluate the clinical efficacy at the test of cure visit (Days 17-24) of oral Augmentin XR 2000/125mg bid for 10 days in patients with ABS.

To assess the safety of oral Augmentin XR 2000/125mg bid for 10 days in patients with ABS.

To assess the incidence of adverse experiences (AEs) in adult patients receiving oral Augmentin XR 2000/125mg bid for 10 days in the treatment of ABS.

To compare the bacteriology obtained from traditional antral puncture sinus aspirates with the bacteriology of aspirates obtained by endoscopically directed aspiration of the middle meatus (in selected centres in the USA only). Bacteriology results from this study subset will be reported separately.

METHODOLOGY

Study Design

This was an open-label, non-comparative, multi-center, Phase III study to evaluate the bacteriological and clinical efficacy and safety of oral Augmentin XR 2000/125mg bid for 10 days in patients with ABS. Patients who were suitable for treatment with an oral antibacterial, who fulfilled the study entry criteria and gave written, dated informed consent were enrolled into the study. Patients were required to attend the clinic four times: screening (Visit 1, Day 0); on-therapy (Visit 2, Day 3-5); end of therapy (Visit 3, Day 12-14) and test of cure (Visit 4, Day 17-24).

The study was designed to enrol approximately 600 patients, in order to obtain at least 10 bacteriologic evaluable patients with penicillin-resistant (MIC $\geq 2\mu\text{g/mL}$) isolates of *S. pneumoniae*. Recruitment was extended to at least 800 patients to ensure that at least 10 patients with PRSP were entered into the study.

Study Population

The study was designed to enrol patients of either gender and at least 16 years of age who presented with ABS signs and symptoms of at least three days (severe cases) to 7 days (mild/moderate cases) but less than 28 days duration (defined by purulent nasal discharge or purulence in the nasal cavity on examination and at least one *major* or two *minor* criteria of ABS). Patients were to have radiological confirmation of ABS.

Primary Efficacy Variable

The primary efficacy variable was the bacteriological response (success or failure) at test of cure (Visit 4).

Secondary Efficacy Variables

The secondary efficacy variables were:

Bacteriological response (success or failure) at the end of therapy (Visit 3).

Clinical response (success or failure) at test of cure (Visit 4).

Clinical response (success or failure) at end of therapy (Visit 3).

Combined clinical and radiological response (success, failure or unable to determine) at test of cure (Visit 4).

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Patient Disposition

The numbers of patients who were enrolled, received at least one dose of study medication and completed the study, together with the numbers of patients eligible for the various ITT and PP populations, are tabulated in Table 1.

Table 1: Patient Disposition (All Enrolled Patients)

Population	Augmentin XR 2000/125mg bid	
	n	
Enrolled	861	
Received Study Medication (ITT/Safety)	859	
Completed Study	803	
Clinical PP End of Therapy	763	
Clinical PP Test of Cure	751	
Bacteriology ITT	415	
Bacteriology PP End of Therapy	378	
Bacteriology PP Test of Cure	372	

Note: This table includes patients evaluated by all the investigators.

Demographic Characteristics

The demographic characteristics in the ITT and Bacteriology ITT populations are shown in Table 2.

Table 2: Demographic Characteristics (ITT and Bacteriology ITT Populations)

Demographic Characteristic	Augmentin XR 2000/125mg bid	
	ITT N=859	Bacteriology ITT N=415
Gender: n (%)		
Male	378 (44.0)	191 (46.0)
Female	481 (56.0)	224 (54.0)
Age (yr)		
Mean (SD)	40.6 (13.6)	40.7 (13.9)
Range	16-83	16-83
Race n (%)		
White	730 (85.0)	347 (83.6)
Black	86 (10.0)	50 (12.0)
Oriental	3 (0.3)	1 (0.2)
Other	40* (4.7)	17** (4.1)
Weight (kg)†		
Mean (SD)	77.9 (18.8)	77.2 (17.8)
Range	42.0-181.8	42.0-157.7
Height (cm)		
Mean (SD)	170.4 (9.6)	170.8 (9.3)
Range	140.8-208.3	140.8-195.6

Sponsor's Table:

* The other races, as recorded by the investigator, were Hispanic (32 patients), Asian Indian (4 patients), Native American (2 patients), Cuban (1 patient) and Pakistani (1 patient).

** The other races, as recorded by the investigator, were Hispanic (15 patients), Asian Indian (1 patient) and Pakistani (1 patient).

† Weight was unavailable for one patient, 551.032.05910

Statistical Reviewer's Comments:

In total, 861 patients were enrolled into the study. Of these 861 patients, 859 patients received study medication and were therefore included in the ITT population. According to the sponsor, one patient (551.401.04816) was enrolled but withdrew from the study before receiving study medication as the patient refused to take study medication. The other patient (551.406.04944) was not known to have taken study medication. The patient attended Visit 1 but did not return for subsequent study visits, did not return study medication and was considered 'lost to follow up'. These two patients were excluded from the ITT and Bacteriology ITT populations.

Based on the demographic details, there was a higher proportion of females than males in the ITT population and the majority of the patients were white. The mean age of the patients was 40.6 years

RESULTS

EFFICACY

Table 3: Initial Pathogen Bacteriological Outcome at Test of Cure (For all Pathogens Combined and Key Pathogens) (Bacteriology ITT Population)

Initial Pathogen	Bacteriological Outcome	Augmentin XR 2000/125mg bid	
		n	(%)
N=415			
All Pathogens	<i>n</i> *	521	
	Eradication	11	(2.1)
	Presumed Eradication	448	(86.0)
	Failure	4	(0.8)
	Presumed Failure	33	(6.3)
	Unable to Determine**	25	(4.8)
<i>S. pneumoniae</i>	<i>n</i> *	113	
	Eradication	2	(1.8)
	Presumed Eradication	103	(91.2)
	Presumed Failure	3	(2.7)
	Unable to Determine**	5	(4.4)
<i>H. influenzae</i>	<i>n</i> *	95	
	Eradication	1	(1.1)
	Presumed Eradication	81	(85.3)
	Failure	3	(3.2)
	Presumed Failure	6	(6.3)
	Unable to Determine**	4	(4.2)
<i>M. catarrhalis</i>	<i>n</i> *	44	

	Eradication	3	(6.8)
	Presumed Eradication	38	(86.4)
	Presumed Failure	2	(4.5)
	Unable to Determine**	1	(2.3)
<i>K. pneumoniae</i>	<i>n</i> *	37	
	Presumed Eradication	34	(91.9)
	Presumed Failure	2	(5.4)
	Unable to Determine**	1	(2.7)
<i>H. parainfluenzae</i>	<i>n</i> *	25	
	Eradication	1	(4.0)
	Presumed Eradication	18	(72.0)
	Presumed Failure	4	(16.0)
	Unable to Determine**	2	(8.0)
MSSA	<i>n</i> *	25	
	Presumed Eradication	22	(88.0)
	Presumed Failure	1	(4.0)
	Unable to Determine**	2	(8.0)

Sponsor's Table

**n* = Total number of pathogens; *n* (%) = number (%) of pathogens with a specified outcome

** Patients who had pathogens with a bacteriological outcome of unable to determine are included in the Bacteriology PP population at test of cure under the following circumstances.

- the patient had one or more initial pathogens which were eradicated/presumed eradicated at end of therapy, AND

- one or more initial pathogens which were persistent/presumed persistent at end of therapy OR one or more superinfecting pathogens at end of therapy, AND

- a bacteriological outcome of unable to determine at test of cure for the pathogen that was eradicated/presumed eradicated at end of therapy (eg because the patient was lost to follow-up).

Note: Patients with bacteriological outcomes in this table are not mutually exclusive.

Statistical Reviewer's Comments:

Based on the sponsor's table 3, in the Bacteriology ITT population, 88.1% (2.1% eradication and 86.0% presumed eradication) of the initial pathogens were either 'eradicated' or 'presumed eradicated' at test of cure. Only 10 PRSPs isolates were (small number of isolates) seen at the screening, all had a bacteriological outcome of 'presumed eradication' at test of cure.

There were three patients in the Bacteriology ITT population with new pathogens at test of cure. One patient had two new pathogens, *Enterococcus faecalis* (amoxicillin/clavulanic acid MIC of 1ug/mL), and *Serratia marcescens* (amoxicillin/clavulanic acid MIC > 16ug/mL), while two patients each had a new pathogen of *M. catarrhalis* (amoxicillin/clavulanic acid MIC of 0.03ug/mL and 0.12ug/mL, respectively). All three patients were also included in the Bacteriology PP population.

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Table 4: Per Patient Bacteriological Response at Test of Cure (Bacteriology ITT and Bacteriology PP Test of Cure Populations) :

Excluding the investigators

Bacteriological Response	Augmentin XR 2000/125mg bid
Bacteriology ITT Population	N=370
Success, n (%)	325(87.8)
Failure, n (%)	45(12.2)
Known Failure	26 (7.0)
Unable to Determine*	19 (5.1)
95% CI For Success Rate	84.0, 90.9
Bacteriology PP Test of Cure Population	N=330
Success, n (%)	308 (93.3)
Failure, n (%)	22 (6.7)
95% CI For Success Rate	89.9, 95.7

* These 19 patients were excluded from the Bacteriology PP test of cure population because of a bacteriological outcome for all initial pathogens of unable to determine.

Statistical Reviewer's Comments:

Excluding the problematic investigators, the per patient bacteriological success rate at test of cure was 87.8% in the Bacteriology ITT population and 93.3 % in the Bacteriology PP test of cure population.

Table 5: Clinical Response at Test of Cure (ITT and Clinical PP Test of Cure Populations)-Excluding the investigators

Clinical Response	Augmentin XR 2000/125mg bid
ITT Population	N=804
Success, n (%)	707 (87.9)
Failure*, n (%)	97 (12.1)
95% CI for Success Rate	85.4, 90.1
Clinical PP Test of Cure Population	N=700
Success, n (%)	649 (92.7)
Failure, n (%)	51 (7.3)
95% CI for Success Rate	90.5, 94.5

Statistical Reviewer's Comments:

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

SAFETY

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

Table 6 Number (%) of Patients with the Most Frequently Reported Adverse Experiences with a Suspected or Probable Relationship to Study Medication ($\geq 1\%$ of Patients)

Preferred Term	Augmentin XR 2000/125mg bid N=859	
	n	(%)
Patients with at Least One AE with Suspected or Probable Relationship	224	(26.1)
Diarrhoea	131	(15.3)
Nausea	19	(2.2)
Genital Moniliasis	18	(2.1)
Gastrointestinal Disorder NOS	16	(1.9)
Abdominal Pain	14	(1.6)
Flatulence	13	(1.5)
Vaginitis	10	(1.2)

Statistical Reviewer's Comments:

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

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

CONCLUSIONS

This open, non-comparative, multicentre study was designed to assess the clinical and bacteriological efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 10 days in the treatment of patients with acute bacterial sinusitis. The primary endpoint of the study was the bacteriological response rate (success/failure) at test of cure (Day 17-28). Secondary efficacy variables were bacteriological response rate at end of therapy (Day 11-16), clinical response rates at end of therapy and test of cure and combined clinical and radiological response at test of cure.

A total of 861 patients were enrolled in the study and 859 patients received study medication. The USA recruited the largest number of patients overall.

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

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

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

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

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

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

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Thamban Valappil
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