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Study No.: 546
Title: A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin® SR 2000/125mg Twice Daily Versus Oral Augmentin® 875/125mg Twice Daily for 7 Days in the Treatment of Adults with Bacterial Community Acquired Pneumonia
Rationale: The aim of this study was to demonstrate that oral amoxicillin/clavulanate sustained release 2000/125mg twice daily (bid) was at least as clinically and bacteriological effective and as safe as the standard formulation of oral amoxicillin/clavulanate 875/125mg bid in the treatment of community acquired pneumonia (CAP).
Phase: III
Study Period: 2 November 1999 to 31 May 2000.
Study Design: Randomised, multicentre, double-blind, double-dummy, parallel group study. Subjects made four clinic visits: screening (day 0), on therapy, end of therapy (EOT) (Days 8-15) and follow-up (FU) (Days 16-37).
Centres: The study was carried out at 81 centres in Belgium (5 centres), Germany (18 centres), Guatemala (1 centre), Mexico (3 centres) and the USA (54 centres).
Indication: Community acquired pneumonia.
Treatment: Patients received 7 days of oral treatment with amoxicillin/clavulanate SR 2000/125mg bid and amoxicillin/clavulanate placebo bid or amoxicillin/clavulanate 875/125mg bid and amoxicillin/clavulanate SR-placebo bid.
Objectives: The primary objective was to demonstrate that oral amoxicillin/clavulanate SR 2000/125mg twice daily for 7 days was at least as effective clinically as oral amoxicillin/clavulanate 875/125mg twice daily for 7 days in the treatment of CAP in adults. The secondary objective was to evaluate the bacteriological efficacy and safety of oral amoxicillin/clavulanate SR 2000/125mg twice daily for 7 days and oral amoxicillin/clavulanate 875/125mg twice daily for 7 days in the treatment of CAP in adults.
Primary Outcome/Efficacy Variable: The clinical response (success or failure) at FU. Clinical success was defined as sufficient resolution of CAP such that no additional antibacterial therapy for CAP was indicated. Clinical failure was recorded when there was insufficient improvement of CAP at end of therapy, requiring additional antibacterial therapy. Clinical failure at follow-up was defined as the reappearance or deterioration of CAP following clinical success at end of therapy. If a patient was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits.
Secondary Outcome/Efficacy Variable(s): Clinical response (success or failure) at EOT. Bacteriological response (success or failure) at FU. Bacteriological response (success or failure) at EOT. Radiological response (success, failure or unable to determine) at FU. Radiological response (success, failure or unable to determine) at EOT. Therapeutic response (success or failure) at FU. Therapeutic response (success or failure) at EOT. Bacteriological success was defined as the eradication or, in the absence of an evaluable repeat culture sample, clinical evidence of eradication of the initial screening pathogen without superinfection or new infection. Bacteriological failure was defined as the persistence or recurrence of the initial screening pathogen, or the presence of a new pathogen in a repeat culture sample. For patients with no repeat culture sample available, bacteriological failure was presumed if clinical signs and symptoms persisted to a degree that necessitated further antibacterial therapy for CAP. If a patient was deemed to be a bacteriological failure at any stage, this outcome was carried forward to all further visits. Radiological response was evaluated by comparing postero-anterior and lateral view chest radiographs with the baseline radiograph. Radiological success was defined as an improvement from the baseline radiograph. Radiological failure was defined as worsening or no change from baseline radiograph. If radiological outcome could not be determined from the repeat radiograph, success or failure was presumed based on clinical outcome. Radiological response to study treatment was evaluated at EOT only for those patients who were clinical failures or withdrew at or before this visit, and at follow-up for all other patients. Therapeutic response was based on combined clinical and bacteriological response.
Statistical Methods: The safety/intent-to-treat (ITT) population included all randomised patients who took at least one dose of study medication. The clinical per-protocol (PP) population was a subset of ITT that excluded patients who

violated any aspect of the protocol to an extent that may affect the assessment of treatment efficacy. The bacteriology PP population included all patients who had at least one typical pre-therapy pathogen identified at screening, but excluded patients who violated any aspect of the protocol to an extent that may affect the assessment of treatment efficacy.

The primary efficacy analysis was based on an unstratified comparison of clinical response proportions between the treatment groups in the clinical PP population. Two-sided 95% confidence intervals (CIs) were used to estimate the difference in the proportion of successes between the treatment groups. A conclusion of non-inferior efficacy of amoxicillin/clavulanate SR was drawn if the lower limit of the CI (amoxicillin/clavulanate SR minus amoxicillin/clavulanate) was $\geq -10\%$. All CIs for differences in proportions were calculated using the normal approximation to the binomial distribution. It should be noted that the study was not designed to demonstrate non-inferiority for secondary end-points where the numbers of patients was expected to be too small to draw any conclusions.

Study Population: Males or females, aged at least 16 years with a clinical and radiological diagnosis of CAP based on radiological findings of new or progressive infiltrates or consolidation consistent with pneumonia on a chest x-ray performed within 48 hours prior to study entry and clinical findings of fever plus one or more of the following: new or increased cough, purulent sputum or change in sputum characteristics, auscultatory finding of rales and/or evidence of consolidation, dyspnoea or tachypnoea, hypoxaemia, increased total peripheral white blood cell (WBC) count, $>10,000$ cells/mm³, or $>15\%$ immature neutrophils regardless of total peripheral WBC count, or leucopenia with total WBC count of $<4,500$ cells/mm³. Subjects were excluded if they had known hypersensitivity to study medication, possible risk of drug interactions, known or suspected renal or liver function impairment, complicating infection, disease or underlying medical condition that would compromise efficacy evaluation of treatment, pneumonia due to atypical pathogens, post-obstructive or aspiration pneumonia, or hospital acquired pneumonia diagnosed 48 hours after admission to hospital or hospitalization in the previous two weeks, or more than 24 hours of treatment with any systemic antibiotic for underlying CAP in the previous 7 days prior to enrollment.

	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 875 / 125mg bid
Number of Subjects:		
Planned, N	508	
Randomised, N	255	261
Safety Population, N	255	259
Clinical PP Population at FU, N	204	204
Bacteriological population at FU, N	32	26
Completed, n (%)	227 (89.0)	228 (88.0)
Total Number Subjects Withdrawn, N (%)	28 (11.0)	31 (12.0)
Withdrawn due to Adverse Events, n (%)	10 (3.9)	19 (7.3)
Withdrawn due to Lack of Efficacy, n (%)	2 (0.8)	1 (0.4)
Withdrawn for other reasons, n (%)	16 (6.3)	11 (4.2)
Demographics	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 875 / 125mg bid
N (Safety population)	255	259
Females: Males	125:130	132:127
Mean Age, years (SD)	52.0 (17.8)	52.5 (17.6)
White, n (%)	211 (82.7)	223 (86.1)
Black	20 (7.8)	14 (5.4)
Oriental	3 (1.2)	1 (0.4)
Other	21 (8.2)	21 (8.1)
Primary Efficacy Results: Clinical PP Population		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=204)	Amoxicillin / clavulanate 875 / 125mg bid (N=204)
Clinical Response at FU		
Success, n (%)	176 (86.3)	186 (91.2)
Failure, n (%)	28 (13.7)	18 (8.8)
Treatment Difference % (Amox/clav SR – Amox/clav)	-4.9	
95% CI	-11.0, 1.2	
p-value	Not applicable	

Secondary Outcome Variable(s):		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 875 / 125mg bid
Clinical Response at EOT: Clinical PP Population		
	N=221	N=219
Success, n (%)	200 (90.5)	207 (94.5)
Failure, n (%)	21 (9.5)	12 (5.5)
Treatment Difference % (Amox/clav SR – Amox/clav)	-4.0	
95% CI	-8.9, 0.9	
Bacteriological Response at FU: Bacteriology PP Population		
	N=32	N=26
Success, n (%)	25 (78.1)	22 (84.6)
Failure, n (%)	7 (21.9)	4 (15.4)
Treatment Difference % (Amox/clav SR – Amox/clav)	-6.5	
95% CI	-26.4, 13.4	
Bacteriological Response at EOT: Bacteriology PP Population		
	N=33	N=26
Success n (%)	28 (84.8)	24 (92.3)
Failure n (%)	5 (15.2)	2 (7.7)
Treatment Difference % (Amox/clav SR – Amox/clav)	-7.5	
95% CI	-23.4, 8.5	
Radiological Response at FU: Clinical PP Population		
	N=204	N=204
Success, n (%)	173 (84.8)	184 (90.2)
Failure, n (%)	8 (3.9)	7 (3.4)
Unable to Determine, n (%)	23 (11.3)	13 (6.4)
Treatment Difference % (Amox/clav SR – Amox/clav)	-5.4	
95% CI	-11.8, 1.0	
Radiological Response at EOT: Clinical PP Population		
	N=221	N=219
Success, n (%)	188 (85.1)	197 (90.0)
Failure, n (%)	25 (11.3)	13 (5.9)
Unable to Determine, n (%)	8 (3.6)	9 (4.1)
Treatment Difference % (Amox/clav SR – Amox/clav)	-4.9	
95% CI	-11.0, 1.3	
Therapeutic Response at FU: Clinical PP Population		
	N=32	N=26
Success, n (%)	25 (78.1)	22 (84.6)
Failure, n (%)	7 (21.9)	4 (15.4)
Therapeutic Response at EOT: Clinical PP Population		
	N=33	N=26
Success, n (%)	28 (84.8)	24 (92.3)
Failure, n (%)	5 (15.2)	2 (7.7)
Safety Population –An adverse event (AE) occurring during the interval on therapy and within 30 days post therapy was defined as an AE which started at anytime from the date of the screening visit up to and including 30 days after the last day of study medication. A serious adverse event (SAE) occurring during the interval on therapy and within 30 days post therapy was defined as an SAE which started at anytime from the date of the screening visit up to and including 30 days after the last day of study medication.		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=255)	Amoxicillin / clavulanate 875 / 125mg bid (N=259)
Most Frequent Adverse Events – On-Therapy and Within 30 Days Post-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	126 (49.4)	133 (51.4)
Diarrhoea	46 (18.0)	37 (14.3)

Headache	11 (4.3)	13 (5.0)
Nausea	11 (4.3)	14 (5.4)
Rhinitis	7 (2.7)	5 (1.9)
Sinusitis	6 (2.4)	5 (1.9)
Vomiting	4 (1.6)	7 (2.7)
Abdominal pain	4 (1.6)	6 (2.3)
Insomnia	4 (1.6)	4 (1.5)
Injury	4 (1.6)	3 (1.2)
Mouth dry	4 (1.6)	3 (1.2)
Constipation	4 (1.6)	2 (0.8)
Dyspepsia	4 (1.6)	2 (0.8)
Rash	4 (1.6)	2 (0.8)
Upper respiratory tract infection	4 (1.6)	2 (0.8)
Pneumonia	3 (1.2)	4 (1.5)
Bronchitis	2 (0.8)	4 (1.5)
Dizziness	2 (0.8)	4 (1.5)
Pruritus	2 (0.8)	4 (1.5)
Oedema dependent	1 (0.4)	4 (1.5)
Pain	1 (0.4)	4 (1.5)
Pleural effusion	1 (0.4)	4 (1.5)
Serum glutamic pyruvic transaminase (SGPT) increased	1 (0.4)	4 (1.5)
Serious Adverse Events - On-Therapy Plus 30 Days Post-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=255)	Amoxicillin / clavulanate 875 / 125mg bid (N=259)
	n (%) [related]	n (%) [related]
Subjects with fatal and non-fatal SAEs, n (%)	15 (5.9) [2]	19 (7.3) [1]
Pneumonia	3 (1.2) [1]	4 (1.5) [1]
Pulmonary carcinoma	2 (0.8) [0]	1 (0.4) [0]
Myocardial infarction	1 (0.4) [0]	1 (0.4) [0]
Respiratory insufficiency	1 (0.4) [0]	1 (0.4) [0]
Asthenia	1 (0.4) [0]	0
Asthma	1 (0.4) [0]	0
Chest pain	1 (0.4) [0]	0
Chronic obstructive airways disease	1 (0.4) [0]	0
Diarrhoea	1 (0.4) [1]	0
Diverticulitis	1 (0.4) [0]	0
Left cardiac failure	1 (0.4) [0]	0
Malignant skin neoplasm	1 (0.4) [0]	0
Meningitis	1 (0.4) [0]	0
Respiratory disorder	1 (0.4) [0]	0
Thrombophlebitis	1 (0.4) [0]	0
Cardiac failure	0	3 (1.2) [0]
Therapeutic response increased ¹	0	3 (1.2) [0]
Pleural effusion	0	2 (0.8) [0]
Aggravated diabetes mellitus	0	1 (0.4) [0]
Cardiac arrest	0	1 (0.4) [0]
Cellulitis	0	1 (0.4) [0]
Gastrointestinal haemorrhage	0	1 (0.4) [0]
Grand mal convulsions	0	1 (0.4) [0]
Hypertension	0	1 (0.4) [0]
Hypoxia	0	1 (0.4) [0]
Tuberculosis infection	0	1 (0.4) [0]
Neoplasm,(lung) not otherwise specified	0	1 (0.4) [0]

<i>Pneumocystis carinii</i> infection	0	1 (0.4) [0]
Pulmonary oedema	0	1 (0.4) [0]
Rectum haemorrhage	0	1 (0.4) [0]
Asymptomatic overdose		
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	2 (0.8) [0]	1 (0.4) [0]
Myocardial infarction	1 (0.4) [0]	0
Left cardiac failure	1 (0.4) [0]	0
Cardiac arrest	0	1 (0.4) [0]

Conclusion:

See publications below.

Publications:

File T, Garau J, Jacobs MR, Wynne B, Berkowitz E, Twynholm M. Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg in the treatment of community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae*, including penicillin-resistant strains. *Int J Antimicrob Agents* 2005; 25(2):110–119.

Garau J, File T, Jacobs MR, Poole MD, Wynne B, The 546–551, 566, 557 and 592 Clinical Study Groups. Efficacy of amoxicillin/clavulanate (AMX/CA) 2000/125 mg b.i.d. against *Streptococcus pneumoniae* non-susceptible to AMX. Abstracts from the 4th International Meeting on the Therapy of Infections, Florence, Italy. October 2002, page 71, Abstract A5.

File T, Jacobs MR, Poole MD, Wynne B. Pharmacokinetically enhanced amoxicillin/clavulanate against *Streptococcus pneumoniae* (Sp) in respiratory tract infections (RTIs). Abstracts from the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, USA. September 2002, page 359, Abstract L-990.

File T, Jacobs MR, Poole MD, Wynne B. Clinical efficacy of pharmacokinetically enhanced amoxicillin/clavulanate (AMX/CA) vs comparators against *Streptococcus pneumoniae* (Sp) in respiratory tract infections (RTIs). Abstracts from the 2nd Forum on Respiratory Tract Infections, Monte Carlo, Monaco. February 2002, page 62, Abstract P4.

Garau J, Jacobs MR, Wynne B, Berkowitz E, Twynholm M. Pharmacokinetically enhanced amoxicillin/clavulanate (AMX/CA) 2000/125 mg in the treatment of community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) caused by *Streptococcus pneumoniae*. Abstracts from the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, USA. September 2003, page 422, Abstract L-1382.

S. Miller, M. Twynholm, E. Berkowitz, S. Gormley, A. White, L.A. Miller, C. Jakielaszek. Bacteriological outcomes with pharmacokinetically enhanced amoxicillin/clavulanate (2000/125 mg) in patients with community-acquired respiratory infection caused by *Streptococcus pneumoniae*, including drug-resistant (DRSP) strains. Abstracts from the 15th European Congress of Clinical Microbiology and Infectious Diseases, April 2005.

Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate (2,000/125 milligrams) versus those of amoxicillin-clavulanate (875/125 milligrams), both given twice daily for 7 days, in treatment of bacterial community-acquired pneumonia in adults. File, T. M. Jr, Lode, H., Kurz, H., Kozak, R., Xie, H., and Berkowitz, E. *Antimicrob Agents Chemother* 2004; 48(9):3323-31

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