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Study No.: 556
Title: A randomised, double-blind, double-dummy, multicentre, parallel group study to assess the efficacy and safety of oral amoxicillin/clavulanate (Augmentin SR) 2000/125mg twice daily for 10 days versus oral amoxicillin/clavulanate 1000/125mg three times daily for 10 days for the treatment of bacterial community acquired pneumonia in adults.
Rationale: The aim of this study was to demonstrate that oral amoxicillin/clavulanate sustained release 2000/125mg twice daily (bid) for 10 days was at least as clinically and bacteriologically effective and safe as the standard formulation of oral amoxicillin/clavulanate 1000/125mg three times daily (tid) for 10 days in the treatment of community acquired pneumonia (CAP).
Phase: III
Study Period: 15 November 1999 to 1 June 2000.
Study Design: Randomised, double-blind, double-dummy, multi-centre, parallel group study. Subjects made four clinic visits: screening (day 0), on therapy, end of therapy (EOT) (Days 11-17) and follow-up (FU) (Days 18-39).
Centres: The study was carried out at 77 centres 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).
Indication: Community acquired pneumonia.
Treatment: Subjects received 10 days of oral treatment with amoxicillin/clavulanate SR 2000/125mg twice daily (bid) or amoxicillin/clavulanate 1000/125mg three times daily (tid).
Objectives: The primary objective was to demonstrate that oral amoxicillin/clavulanate SR 2000/125mg bid for 10 days is at least as effective clinically as oral amoxicillin/clavulanate 1000/125mg tid for 10 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 10 days and oral amoxicillin/clavulanate 1000/125mg three times daily for 10 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 the end of therapy visit (Visit 3, Day 11-17). Bacteriological response (success or failure) at the follow-up 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 follow-up visit (Visit 4). Radiological response (success, failure or unable to determine) at the end of therapy visit (Visit 3). Therapeutic response (combined clinical and bacteriological response – success or failure) at follow-up (Visit 4). Therapeutic response (combined clinical and bacteriological response – success or failure) at end of therapy (Visit 3) 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 a 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. The therapeutic response is a combination of the clinical and bacteriological response for patients in the bacteriological population.
Statistical Methods: The safety population included all randomised patients who took at least one dose of study

<p>medication. The clinical per-protocol (PP) population consists of the safety population but excludes patients who violated any aspect of the protocol to an extent that may have affected treatment efficacy. The bacteriology PP population included the clinical PP population who had at least one pre-therapy pathogen identified at screening. The primary analysis was based on the clinical response at the test of cure in the clinical PP population. The efficacy analyses were based on an unstratified comparison of proportions between the treatment groups. 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 from the primary analysis (amoxicillin/clavulanate SR minus amoxicillin/clavulanate 1g) was \geq-15%. 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.</p>		
<p>Study Population: Subjects of either gender, aged at least 18 years with a diagnosis of radiologically confirmed 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, with a fever and at least two of the following pre-defined respiratory signs/ symptoms: new or increased cough, purulent sputum or change in sputum characteristics, auscultatory findings of rales and/or evidence of pulmonary consolidation, dyspnoea. 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 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, more than 24 hours of treatment with any systemic antibiotic for underlying CAP or failed therapy with a macrolide or first generation cephalosporin (as first line treatment for at least 48 hours) provided they had a Gram-positive cocci or <i>Haemophilus</i> or <i>Moraxella</i> on direct examination of a sputum sample.</p>		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 1000 / 125mg tid
Number of Subjects:		
Planned, N	320	
Randomised, N	169	178
Safety Population, N	169	175
Clinical PP Population at Follow-up, N	118	114
Bacteriology PP Population at Test of Cure, N	32	32
Completed, n (% of Safety population)	141 (83.4)	152 (86.9)
Total Number Subjects Withdrawn, n (%)	28 (16.6)	23 (13.1)
Withdrawn due to Adverse Events, n (%)	9 (5.3)	7 (4.0)
Withdrawn due to Lack of Efficacy, n (%)	5 (3.0)	5 (2.9)
Withdrawn for Other Reasons, n (%)	14 (8.3)	11 (6.3)
Demographics	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 1000 / 125mg tid
N (Safety Population)	169	175
Females: Males	76:93	72:103
Mean Age, years (SD)	57.3 (18.6)	56.9 (19.1)
White, n (%)	156 (92.3)	165 (94.3)
Primary Efficacy Results: Clinical PP Population		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=118)	Amoxicillin / clavulanate 1000 / 125mg tid (N=114)
Clinical Response at Follow-up		
Success, n (%)	108 (91.5)	106 (93.0)
Failure, n (%)	10 (8.5)	8 (7.0)
Treatment Difference % (Amox/clav SR – Amox/clav)	-1.5	
95% CI	-8.3, 5.4	
p-value	Not applicable	
Secondary Outcome Variable(s):		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 1000 / 125mg tid
Clinical Response at End of Therapy: Clinical PP Population		

	N=129	N=119
Success, n (%)	120 (93.0)	111 (93.3)
Failure, n (%)	9 (7.0)	8 (6.7)
Treatment Difference % (Amox/clav SR – Amox/clav)	-0.3	
95% CI	-6.5, 6.0	
Bacteriological Response at Follow-up: Bacteriological PP Population		
	N=32	N=32
Success n (%)	29 (90.6)	27 (84.4)
Failure n (%)	3 (9.4)	5 (15.6)
Treatment Difference % (Amox/clav SR – Amox/clav)	6.3	
95% CI	-9.9, 22.4	
Bacteriological Response at End of Therapy: Bacteriological PP Population		
	N=33	N=34
Success, n (%)	30 (90.9)	29 (85.3)
Failure, n (%)	3 (9.1)	5 (14.7)
Treatment Difference % (Amox/clav SR – Amox/clav)	5.6	
95% CI	-9.8, 21.0	
Radiological Response at Follow-up: Clinical PP Population		
	N=118	N=114
Success n (%)	109 (92.4)	107 (93.9)
Failure n (%)	2 (1.7)	0
Unable to determine n (%)	7 (5.9)	7 (6.1)
Treatment Difference % (Amox/clav SR – Amox/clav)	-1.5	
95% CI	-8.0, 5.0	
Radiological Response at End of Therapy: Clinical PP Population		
	N=129	N=119
Success, n (%)	113 (87.6)	109 (91.6)
Failure, n (%)	9 (7.0)	4 (3.4)
Unable to determine n (%)	7 (5.4)	6 (5.0)
Treatment Difference % (Amox/clav SR – Amox/clav)	-4.0	
95% CI	-11.6, 3.6	
Therapeutic Response at Follow-up : Bacteriology PP Population		
	N=32	N=32
Success, n (%)	29 (90.6)	27 (84.4)
Failure, n (%)	3 (9.4)	5 (15.6)
Therapeutic Response at End of Therapy : Bacteriology PP Population		
	N=33	N=34
Success, n (%)	30 (90.9)	29 (85.3)
Failure, n (%)	3 (9.1)	5 (14.7)
Safety Results: 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=169)	Amoxicillin / clavulanate 1000 / 125mg tid (N=175)
Most Frequent Adverse Events – On-Therapy Within 30 Days Post-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	81(47.9)	94 (53.7)
Diarrhea	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)
Angina pectoris	3 (1.8)	2 (1.1)
Anxiety	3 (1.8)	3 (1.7)
Arthralgia	3 (1.8)	0
Dyspepsia	3 (1.8)	3 (1.7)
Moniliasis	3 (1.8)	6 (3.4)
Nausea	3 (1.8)	5 (2.9)
Serum glutamic oxaloacetic transaminase (SGOT) increased	3 (1.8)	2 (1.1)
Serum glutamic pyruvic transaminase (SGPT) increased	3 (1.8)	3 (1.7)
Vomiting	3 (1.8)	2 (1.1)
Infection fungal	2 (1.2)	4 (2.3)
Fibrillation atrial	1 (0.6)	3 (1.7)
Rash	1 (0.6)	3 (1.7)
Chest pain	0	3 (1.7)
Tachycardia	0	4 (2.3)
Serious Adverse Events - On-Therapy Within 30 Days Post-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=169)	Amoxicillin / clavulanate 1000 / 125mg tid (N=175)
	n (%) [related]	n (%) [related]
Subjects with fatal and non-fatal SAEs, n (%)	12 (7.1) [0]	10 (5.7) [2]
Pneumonia	3 (1.8) [0]	4 (2.3) [1]
Respiratory disorder	3 (1.8) [0]	0
Abdominal pain	1 (0.6) [0]	0
Abnormal renal function	1 (0.6) [0]	0
Bronchitis	1 (0.6) [0]	0
Cardiac failure	1 (0.6) [0]	0
Cerebrovascular disorder	1 (0.6) [0]	0
Dyspnoea	1 (0.6) [0]	0
Fever	1 (0.6) [0]	0
Neoplasm (non-specific)	1 (0.6) [0]	1 (0.6) [0]
Sepsis	1 (0.6) [0]	1 (0.6) [0]
Abscess	0	1 (0.6) [0]
Aggravated depression	0	1 (0.6) [0]
Pulmonary carcinoma	0	2 (1.1) [0]
Tachycardia	0	1 (0.6) [0]
Therapeutic response increased*	0	1 (0.6) [1]
Withdrawal syndrome (alcohol)	0	1 (0.6) [0]
*asymptomatic overdose		
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	2 (1.2) [0]	0
Cerebrovascular disorder	1 (0.6) [0]	0
Pneumonia (Persistent)	1 (0.6) [0]	0
Neoplasm (non-specific, left lung)	1 (0.6) [0]	0

Conclusion: See publications below.

Publications:
Petitpretz P, Chidiac C, Soriano F, Garau J, Stevenson K, Rouffiac E. The efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate 2000/125 mg, twice daily, versus oral amoxicillin-clavulanate 1000/125 mg, three times daily, for the treatment of bacterial community-acquired pneumonia in adults. <i>Int J Antimicrob Agents</i> 2002; 20(2): 119–29.
Petitpretz P, Chidiac C, Soriano F, Garau J, Stevenson K, Rouffiac E. Efficacy and safety of oral pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg twice daily versus oral amoxicillin/clavulanate 1000/125 mg three times daily for the treatment of bacterial community acquired pneumonia (CAP) in adults. Abstracts from the 2001 Annual Meeting of the European Respiratory Society, Berlin, Germany. September 2001, page 137S, Abstract P920.
File T, Jacobs MR, Poole MD, Wynne B. Outcome of treatment of respiratory tract infections due to <i>Streptococcus pneumoniae</i> , including drug-resistant strains, with pharmacokinetically enhanced amoxicillin/clavulanate. <i>Int J Antimicrob Agents</i> 2002; 20(4): 235–47.
File T, Garau J, Jacobs MR, Wynne B. Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg in the treatment of community-acquired pneumonia (CAP) caused by <i>Streptococcus pneumoniae</i> , including penicillin-resistant strains. <i>Int J Antimicrob Agents</i> 2005; 25(2):110–119.
Garau J, File T, Jacobs MR, Poole MD, Wynne B, The 546–551, 556, 557 and 592 Clinical Study Groups. Efficacy of amoxicillin/clavulanate (AMX/CA) 2000/125 mg b.i.d. against <i>Streptococcus pneumoniae</i> 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 <i>Streptococcus pneumoniae</i> (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 <i>Streptococcus pneumoniae</i> (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 <i>Streptococcus pneumoniae</i> . 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 <i>Streptococcus pneumoniae</i> , including drug-resistant (DRSP) strains Abstracts from the 15th European Congress of Clinical Microbiology and Infectious Diseases, April 2005.
File T, Garau J, Jacobs MR, Wynne B. Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg in the treatment of community-acquired pneumonia (CAP) caused by <i>Streptococcus pneumoniae</i> , including penicillin-resistant strains. Abstracts from the 41st Annual Meeting of the Infectious Disease Society of America, San Francisco, USA. October 2003, page 84, Abstract 303.

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