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Study No.: 557
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 Three Times Daily for 7 or 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 (Augmentin SR) 2000/125mg twice daily (bid) was at least as clinically and bacteriologically effective and as safe as the standard formulation of oral amoxicillin/clavulanate 875/125mg three times daily (tid) in the treatment of community acquired pneumonia (CAP).
Phase: III
Study Period: 20 January 2000 to 2 January 2001.
Study Design: Randomised, double-blind, double-dummy, multicentre, parallel group study. Subjects made four clinic visits: screening (day 0), on therapy, end of therapy (EOT) (Days 8-17) and follow-up (FU) (Days 18-39).
Centres: 32 centres in Italy (12 centres) and Spain (20 centres).
Indication: Community acquired pneumonia.
Treatment: Subjects received 7 or 10 days of oral treatment with amoxicillin/clavulanate SR 2000/125mg bid and oral amoxicillin/clavulanate placebo tid or amoxicillin/clavulanate 875/125mg tid and amoxicillin/clavulanate SR placebo bid.
Objectives: The primary objective was to demonstrate that oral amoxicillin/clavulanate SR 2000/125mg bid was at least as effective as oral amoxicillin/clavulanate 875/125mg tid for 7 or 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 7 or 10 days and oral amoxicillin/clavulanate 875/125mg three times daily for 7 or 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 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 subjects 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 subjects who were clinical failures or withdrew at or before this visit, and at follow-up for all other subjects. Therapeutic response was based on combined clinical and bacteriological response.
Statistical Methods: The safety/intent-to-treat (ITT) population included all randomised subjects who took at least one dose of study medication. The clinical per-protocol (PP) population was a subset of ITT that excluded subjects who violated any aspect of the protocol to an extent that may affect the assessment of treatment efficacy. The bacteriology

<p>PP population included all patients who had at least one typical pre-therapy pathogen identified at screening, but excluded subjects who violated any aspect of the protocol to an extent that may affect the assessment of treatment efficacy.</p> <p>The primary efficacy analysis was based on an unstratified comparison of clinical response proportions between the treatment groups for 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 was drawn if the lower limit of the CI (amoxicillin/clavulanate SR minus amoxicillin/clavulanate) 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 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 findings of rales and/or evidence of pulmonary 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.</p>		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 875 / 125mg tid
Number of Subjects:		
Planned, N	320	
Randomised, N	158	162
Safety Population, N	158	161
Clinical PP Population at FU, N	114	116
Bacteriological PP Population at FU, N	20	22
Completed, n (% of Safety population)	136 (86.1)	133 (82.6)
Total Number Subjects Withdrawn, n (%)	22 (13.9)	28 (17.4)
Withdrawn due to Adverse Events, n (%)	11 (7.0)	9 (5.6)
Withdrawn due to Lack of Efficacy, n (%)	5 (3.2)	8 (5.0)
Withdrawn for Other Reasons, n (%)	6 (3.8)	11 (6.8)
Demographics	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 875 / 125mg tid
N (Safety Population)	158	161
Females: Males	49:109	51:110
Mean Age, years (SD)	56.6 (20.1)	53.5 (19.5)
White, n (%)	154 (97.5)	159 (98.8)
Primary Efficacy Results: Clinical PP Population		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=114)	Amoxicillin / clavulanate 875 / 125mg tid (N=116)
Clinical Response at FU		
Success, n (%)	108 (94.7)	103 (88.8)
Failure, n (%)	6 (5.3)	13 (11.2)
Treatment Difference % (Amox/clav SR – Amox/clav)	5.9	
95% CI	-1.1, 13.0	
p-value	Not applicable	
Secondary Outcome Variable(s):		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Amoxicillin / clavulanate 875 / 125mg tid
Clinical Response at EOT: Clinical PP Population		
	N=126	N=128

Success, n (%)	121 (96.0)	118 (92.2)
Failure, n (%)	5 (4.0)	10 (7.8)
Treatment Difference % (Amox/clav SR – Amox/clav)	3.8	
95% CI	-1.9, 9.6	
Bacteriological Response at FU: Bacteriology PP Population		
	N=20	N=22
Success, n (%)	17 (85.0)	17 (77.3)
Failure, n (%)	3 (15.0)	5 (22.7)
Treatment Difference % (Amox/clav SR – Amox/clav)	7.7	
95% CI	-15.8, 31.2	
Bacteriological Response at EOT: Bacteriology PP Population		
	N=23	N=26
Success, n (%)	21 (91.3)	21 (80.8)
Failure, n (%)	2 (8.7)	5 (19.2)
Treatment Difference % (Amox/clav SR – Amox/clav)	10.5	
95% CI	-8.5, 29.6	
Radiological Response at FU: Clinical PP Population		
	N=114	N=116
Success, n (%)	108 (94.7)	102 (87.9)
Failure, n (%)	1 (0.9)	4 (3.4)
Unable to Determine, n (%)	5 (4.4)	10 (8.6)
Treatment Difference % (Amox/clav SR – Amox/clav)	6.8	
95% CI	-0.4, 14.0	
Radiological Response at EOT: Clinical PP Population		
	N=126	N=128
Success, n (%)	111 (88.1)	111 (86.7)
Failure, n (%)	11 (8.7)	13 (10.2)
Unable to Determine, n (%)	4 (3.2)	4 (3.1)
Treatment Difference % (Amox/clav SR – Amox/clav)	1.4	
95% CI	-6.8, 9.5	
Therapeutic Response at FU: Bacteriology PP Population		
	N=20	N=22
Success, n (%)	17 (85.0)	17 (77.3)
Failure, n (%)	3 (15.0)	5 (22.7)
Therapeutic Response at EOT: Bacteriology PP Population		
	N=23	N=26
Success, n (%)	21 (91.3)	20 (76.93)
Failure, n (%)	2 (8.7)	6 (23.1)
Safety Results: 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=158)	Amoxicillin / clavulanate 875 / 125mg tid (N=161)
Most Frequent Adverse Events – On-Therapy and within 30 Days Post-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	98 (62.0)	93 (57.8)
Diarrhoea	29 (18.4)	24 (14.9)
Headache	13 (8.2)	4 (2.5)
Abdominal pain	8 (5.1)	8 (5.0)
Haemoptysis	6 (3.8)	4 (2.5)
Pleural effusion	6 (3.8)	4 (2.5)
Pneumonia	6 (3.8)	8 (5.0)

Vomiting	6 (3.8)	7 (4.3)
Phlebitis	5 (3.2)	4 (2.5)
Asthenia	4 (2.5)	2 (1.2)
Bronchitis	4 (2.5)	9 (5.6)
Dyspepsia	4 (2.5)	4 (2.5)
Hepatic enzymes increased	4 (2.5)	5 (3.1)
Herpes simplex	4 (2.5)	6 (3.7)
Arthralgia	3 (1.9)	4 (2.5)
Insomnia	2 (1.3)	4 (2.5)
Respiratory disorder	2 (1.3)	5 (3.1)
Constipation	1 (0.6)	4 (2.5)
Haematuria	1 (0.6)	5 (3.1)
Upper respiratory tract infection	0	4 (2.5)
Serious Adverse Events (SAEs) - On-Therapy and Within 30 Days Post-Therapy n (%) [n considered by the investigator to be related to study medication]		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=158)	Amoxicillin / clavulanate 875 / 125mg tid (N=161)
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	17 (10.8) [5]	18 (11.2) [0]
Pneumonia	6 (3.8) [4]	6 (3.7) [0]
Pleural effusion	2 (1.3) [0]	1 (0.6) [0]
Pulmonary carcinoma	2 (1.3) [0]	0
Chronic obstructive airways disease	1 (0.6) [0]	1 (0.6) [0]
Confusion	1 (0.6) [0]	0
Fever	1 (0.6) [0]	1 (0.6) [0]
Hepatitis cholestatic	1 (0.6) [0]	0
Neoplasm, (pulmonary) not otherwise specified	1 (0.6) [0]	0
Therapeutic response increased ¹	1 (0.6) [0]	0
Urticaria	1 (0.6) [1]	0
Arthritis	0	1 (0.6) [0]
Cardiac failure	0	1 (0.6) [0]
Embolism pulmonary	0	1 (0.6) [0]
Gastric carcinoma	0	1 (0.6) [0]
Haemoptysis	0	1 (0.6) [0]
Infection tuberculosis	0	1 (0.6) [0]
Lymphoma malignant	0	1 (0.6) [0]
Pulmonary oedema	0	1 (0.6) [0]
Respiratory disorder	0	1 (0.6) [0]
Respiratory insufficiency	0	1 (0.6) [0]
Thrombophlebitis deep	0	1 (0.6) [0]
asymptomatic overdose		
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

See publications below.

Publications:

Garau J, Twynholm M, Garcia-Mendez E, Siquier B, Rivero A and the 557 Clinical Study Group. Oral pharmacokinetically enhanced co-amoxiclav 2000/125 mg, twice daily, compared with co-amoxiclav 875/125 mg, three times daily, in the treatment of community-acquired pneumonia in European adults. J Antimicrob Chemother 2003; 52(5): 826–36.

Garau J, Twynholm M, Garcia-Mendez E. Comparative efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate b.d. versus amoxicillin/clavulanate 875/125 mg t.d.s. in community-acquired pneumonia (CAP).

Abstracts from the 12th European Congress of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect 2002; 8 (Suppl 1): 322. Abstract P1374

File T, Jacobs MR, Poole MD, Wynne B. Outcome of treatment of respiratory tract infections due to Streptococcus pneumoniae, including drug-resistant strains, with pharmacokinetically enhanced amoxicillin/clavulanate. Int J Antimicrob Agents 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 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, 556, 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.

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 Streptococcus pneumoniae, 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.

Bactericidal activity of 2000/125mg sustained-release versus 875/125 mg amoxicillin/clavulanic acid against S. pneumoniae: an amoxi- cillin in vitro pharmacodynamic simulation, Sevillano, D; Calvo, A; Aguilar, L; Alou, L; Giménez, MJ; Valero, E; Prieto, J. Microbiology Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain; Paris; France. 6th European Congress of Chemotherapy and Infection and 24th Interdisciplinary Meeting on Chemotherapy and Infection. 12/1/2004

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