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Study No.: 548
Title: A Randomized, double-blind, double-dummy, multicenter, parallel group study to assess the efficacy and safety of oral <i>Augmentin</i> SR 2000/125mg twice daily for 7 days versus oral clarithromycin 500mg twice daily for 7 days in the treatment of acute exacerbation of chronic bronchitis.
Rationale: The aim of this study was to evaluate whether oral amoxicillin/clavulanate (SR) 2000/125mg twice daily (bid) for 7 days was at least as effective as clarithromycin 500mg bid for 7 days in the treatment of acute exacerbation of chronic bronchitis (AECB).
Phase: III
Study Period: 9 November 1999 to 23 March 2000.
Study Design: Randomized, double-blind, double-dummy, multicenter, parallel group study. Subjects attended five clinic visits: Screening (Visit 1, Days-2 to 1), on-therapy (Visit 2, Days 3 to 5), End of therapy (EOT), (Visit 3, Days 8 to 13), Follow-up (FU), (Visit 4, Days 14 to 23) and long term follow-up (LTFU), (Visit 5, Days 25 to 38).
Centers: The study was conducted in 85 centers in Mexico (1) and US (84).
Indication: Acute exacerbation of chronic bronchitis.
Treatment: Subjects were randomised on a 1:1 basis to receive oral amoxicillin/clavulanate SR 2000/125mg twice daily and oral clarithromycin placebo for 7 days or oral clarithromycin 500mg twice daily and oral amoxicillin/clavulanate SR placebo for 7 days.
Objectives: The primary objective of the study was to demonstrate that oral amoxicillin/clavulanate SR 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 AECB.
Primary Outcome/Efficacy Variable: The clinical response (success or failure) at FU (Visit 4). Clinical success was defined as sufficient resolution of AECB such that no additional antibacterial therapy for AECB was indicated. Clinical failure was recorded when there was insufficient improvement of AECB at EOT requiring additional antibacterial therapy. Clinical failure at FU and LTFU was defined as reappearance or deterioration of AECB following clinical success at previous visits. If a subject 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 (Visit 3). Clinical response (success or failure) at LTFU (Visit 5). Bacteriological response (success or failure) at FU (Visit 4). Bacteriological response (success or failure) at EOT (Visit 3). Bacteriological response (success or failure) at LTFU (Visit 5). Therapeutic response (success or failure) at FU. Therapeutic response (success or failure) at EOT. Therapeutic response (success or failure) at LTFU. Bacteriological success was defined as the eradication or, in the absence of an evaluable repeat culture sample, clinical evidence of eradication of all initial screening pathogens without superinfection or new infection. Bacteriological failure was defined as the persistence or recurrence of an 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 the indication under investigation. If a subject was deemed to be a bacteriological failure at any stage, this outcome was carried forward to all further visits. Therapeutic response was based on combined clinical and bacteriological response.
Statistical Methods: The safety population included all randomised subjects who took at least one dose of study medication. The clinical per-protocol (PP) population was a subset of the safety population that excluded subjects who violated any aspect of the protocol to an extent that may affect treatment efficacy. The bacteriology PP population included all randomised subjects who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening and excluded subjects who violated any aspect of the protocol to an extent that may affect 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 clarithromycin) 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 subjects was too small to draw any conclusions.		
Study Population: Subjects of either gender, at least 40 years of age, with a history of chronic bronchitis 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. Subjects were to have AECB characterized by increased purulent sputum together with increased cough and increased dyspnea and be suitable for oral therapy. Subjects were excluded if they had a known hypersensitivity to study drugs, known or suspected renal or liver function impairment, were immunocompromised, HIV positive with a CD4 count < 200mm ³ or had any complicating disease or infection that would complicate evaluation of study treatment, including pneumonia (clinically and radiologically confirmed), cystic fibrosis, active tuberculosis, bronchiectasis and active pulmonary malignancy. The use of prohibited medications including systemic corticosteroids (>10 mg/day prednisone or equivalent), cisapride, primozide, renal tubular secretion inhibitors such as probenecid and non-sedating anti-histamines such as terfenadine and astemizole was also a basis for exclusion, as was the use of any systemic antibacterial within 7 days prior to study entry.		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Clarithromycin 500mg bid
Number of Subjects:		
Planned, N	300	300
Randomized, N	291	297
Safety Population, N	290	295
Completed, n (% of Safety Population))	253 (87.2)	264 (89.5)
Clinical PP Population at FU	221	240
Bacteriological PP Population at FU	40	41
Total Number Subjects Withdrawn, n (%)	37 (12.8)	31 (10.5)
Withdrawn due to Adverse Events, n (%)	15 (5.2)	11 (3.7)
Withdrawn due to Lack of Efficacy, n (%)	1(0.3)	2 (0.7)
Withdrawn for Other Reasons, n (%)	21 (7.2)	18 (6.1)
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Clarithromycin 500mg bid
Demographics		
N (Safety Population)	290	295
Females: Males	167:123	163:132
Mean Age, years (SD)	57.2 (12.0)	56.7 (12.0)
White, n (%)	254 (87.6)	268 (90.8)
Primary Efficacy Results: Clinical PP Population		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Clarithromycin 500mg bid
Clinical Response at FU	N=221	N=240
Success, n (%)	187 (84.6)	206 (85.8)
Failure, n (%)	34 (15.4)	34 (14.2)
Treatment Difference % (Amox/clav SR – Clari)	-1.2	
95% CI	-7.7, 5.3	
p-value	Not applicable	
Secondary Outcome Variable(s):		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Clarithromycin 500mg bid
Clinical Response at EOT: Clinical PP Population		
	N=233	N=247
Success, n (%)	212 (91.0)	226 (91.5)
Failure, n (%)	21 (9.0)	21 (8.5)
Treatment Difference % (Amox/clav SR – Clari)	-0.5	
95% CI	-5.6, 4.6	
Clinical Response at LTFU: Clinical PP Population		
	N=215	N=231
Success, n (%)	165 (76.7)	187 (81.0)
Failure, n (%)	50 (23.3)	44 (19.0)
Treatment Difference % (Amox/clav SR – Clari)	-4.2	

95% CI	-11.8, 3.4	
Bacteriological Response at FU: Bacteriological PP Population		
	N=40	N=41
Success n (%)	30 (75.0)	32 (78.0)
Failure n (%)	10 (25.0)	9 (22.0)
Treatment Difference % (Amox/clav SR – Clari)	-3.0	
95% CI	-21.5, 15.4	
Bacteriological Response at EOT: Bacteriological PP Population		
	N=47	N=42
Success, n (%)	38 (80.9)	36 (85.7)
Failure, n (%)	9 (19.1)	6 (14.3)
Treatment Difference % (Amox/clav SR – Clarith)	-4.9	
95% CI	-20.3, 10.6	
Bacteriological Response at LTFU: Bacteriological PP Population		
	N=37	N=36
Success, n (%)	25 (67.6)	26 (72.2)
Failure, n (%)	12 (32.4)	10 (27.8)
Treatment Difference % (Amox/clav SR – Clarith)	-4.7	
95% CI	-25.7, 16.4	
Therapeutic Response at FU : Bacteriology PP Population		
	N= 40	N=41
Success, n (%)	30 (75.0)	32 (78.0)
Failure, n (%)	10 (25.0)	9 (22.0)
Therapeutic Response at EOT : Bacteriology PP Population		
	N= 47	N=42
Success, n (%)	36 (76.6)	36 (88.7)
Failure, n (%)	11 (23.4)	6 (14.3)
Therapeutic Response at LTFU : Bacteriology PP Population		
	N= 37	N=36
Success, n (%)	24 (64.9)	26 (72.2)
Failure, n (%)	13 (35.1)	10 (27.8)
Safety Results: 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=290)	Clarithromycin 500mg bid (N=295)
Most Frequent Adverse Events – On-Therapy Plus 30 Days Post-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	191 (65.9)	193 (65.4)
Diarrhea	80 (27.6)	34 (11.5)
Headache	21 (7.2)	15 (5.1)
Nausea	19 (6.6)	20 (6.8)
Moniliasis genital	16 (5.5)	2 (0.7)
Infection viral	12 (4.1)	5 (1.7)
Upper respiratory tract infection	11 (3.8)	3 (1.0)
Rhinitis	10 (3.4)	14 (4.7)
Abdominal pain	9 (3.1)	17 (5.8)
Infection fungal	9 (3.1)	1 (0.3)
Injury	9 (3.1)	7 (2.4)
Vomiting	8 (2.8)	8 (2.7)
Sinusitis	7 (2.4)	12 (4.1)
Pharyngitis	5 (1.7)	10 (3.4)

Flatulence	3 (1.0)	11 (3.7)
Taste perversion	3 (1.0)	34 (11.5)
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=290)	Clarithromycin 500mg bid (N=295)
Subjects with fatal and non-fatal SAEs, n (%)	5 (1.7)	12 (4.1)
	n (%) [related]	n (%) [related]
Abdominal pain	1 (0.3) [1]	0
Alcohol intolerance	1 (0.3) [0]	0
Cyclothymic reaction (bipolar disorder)	1 (0.3) [0]	0
Depression	1 (0.3) [0]	0
Diarrhea	1 (0.3) [1]	0
Injury	1 (0.3) [0]	0
Therapeutic response increased ¹	1 (0.3) [0]	0
Asthma	0	2 (0.7) [0]
Cardiac failure	0	2 (0.7) [0]
Basal cell carcinoma	0	1 (0.3) [0]
Bronchitis	0	1 (0.3) [0]
Cellulitis	0	1 (0.3) [0]
Cerebrovascular disorder	0	1 (0.3) [0]
Chronic obstructive airways disease	0	1 (0.3) [0]
Convulsions	0	1 (0.3) [0]
Gastritis	0	1 (0.3) [1]
Gastrointestinal hemorrhage	0	1 (0.3) [0]
Lymphoma malignant	0	1 (0.3) [0]
Pneumonia	0	1 (0.3) [0]
Subjects with fatal SAEs, n (%)	0	0
Asymptomatic overdose		

<p>Conclusion: See publications below.</p>
<p>Publications:</p>
<p>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.</p>
<p>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.</p>
<p>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.</p>
<p>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.</p>
<p>File T, Sethi S, Jacobs M, Anzueto A, Twynholm M, Pypstra R. Comparative efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate vs levofloxacin in AECB. Abstracts from the 98th Annual Meeting of the American Thoracic Society, Atlanta, GA, USA. May 2002, page B28, Abstract 312.</p>
<p>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.</p>

Date Updated: 30-Oct-2005