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Study No.: 547
Title: An Open, Non-Comparative Multicenter Study to Assess the Efficacy and Safety of Oral <i>Augmentin SR</i> 2000/125 mg Twice Daily for 7 days for the Treatment of Bacterial Community-Acquired Pneumonia in adults.
Rationale: Antibiotic resistance to pathogens commonly implicated in community acquired pneumonia (CAP) has increased worldwide. Augmentin SR was specifically developed to tackle the emerging problem of increased bacterial resistance to penicillin and other antibiotics. The purpose of this study was to examine the clinical and bacteriological efficacy and safety of oral Augmentin SR tablets (pharmacokinetically enhanced amoxicillin/clavulanate) 2000/125mg twice daily (bid) for 10 days, in treating subjects with CAP, and particularly penicillin-resistant <i>Streptococcus pneumoniae</i> (PRSP).
Phase: III
Study Period: 15 November 1999 to 17 November 2003.
Study Design: An open, non-comparative, multicenter study. Subjects were instructed to attend the clinic at the following visits: Screening (Visit 1, day 0), On-Therapy (Visit 2, day 3-5), End of Therapy (Visit 3, day 9-11) and Follow-Up (Visit 4, Day 28-35)
Centers: 182 centers in 22 countries: Bulgaria (5), China (8), Costa Rica (1), Croatia (1), Czech Republic (4), France (23), Hungary (4), Indonesia (2), Ireland (2), Malaysia (1), Mexico (3), Pakistan (2), Philippines (2), Poland (7), Romania (6), Russia (6), Saudi Arabia (1), South Africa (15), Taiwan (9), Thailand (1), Turkey (2) and United States (77).
Indication: Community-Acquired Pneumonia (CAP)
Treatment: Subjects received 7 days of oral treatment with amoxicillin/clavulanate SR 2000/125mg twice daily (bid).
Objectives: The primary objective was to evaluate the bacteriological efficacy of oral amoxicillin/clavulanate SR 2000/125mg bid for 7 days in the treatment of CAP in adults, in particular, with an infection due to PRSP with an amoxicillin ± clavulanic acid minimum inhibitory concentration (MIC) of $\geq 4\mu\text{g/mL}$. The secondary objective was to evaluate the efficacy and safety of oral amoxicillin/clavulanate SR 2000/125mg bid for 7 days in the treatment of CAP in adults.
Primary Outcome/Efficacy Variable: Bacteriological response (success or failure) at the follow up visit (Visit 4). 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 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 the indication under investigation. If a patient was deemed to be a bacteriological failure at any visit, this outcome was carried forward to all further visits.
Secondary Outcome/Efficacy Variable(s): Bacteriological response (success or failure) at the end of therapy visit (Visit 3). Clinical response (success or failure) at the follow up visit (Visit 4). Clinical response (success or failure) at the end of therapy visit (Visit 3). Clinical success was defined as sufficient resolution of signs and symptoms of CAP such that no additional antibacterial therapy for CAP was indicated. Clinical failure was recorded when there was insufficient improvement of signs and symptoms of CAP at the end of therapy visit requiring additional antibacterial therapy. Clinical failure at the follow up visit was defined as reappearance or deterioration of signs and symptoms of CAP following clinical success at the end of therapy visit. If a patient was deemed to be a clinical failure at any visit, this outcome was carried forward to all further visits. 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). Radiological response was evaluated by comparing repeat postero-anterior and lateral view chest radiographs with baseline radiographs. Radiological success was defined as an improvement from baseline radiographs. Radiological failure was defined as worsening or no change from baseline radiographs. If radiological outcome could not be determined from the repeat radiographs, success or failure was presumed based on clinical outcome. Radiological response to study treatment was evaluated at the end of therapy visit only for those subjects who were clinical failures or withdrew at or before this visit, and at the follow up visit for all other subjects.

<p>Statistical Methods: The Intent-to-Treat (ITT) population included all subjects who received study treatment. The Bacteriological ITT population included all subjects who received study treatment, and had at least one typical pre-therapy pathogen identified at screening (most commonly caused by Gram positive and Gram-negative organisms such as <i>S. pneumoniae</i>, <i>S. aureus</i>, <i>H. influenzae</i>, <i>Klebsiella pneumoniae</i>, and <i>M. catarrhalis</i>). The Clinical and Bacteriological Per-Protocol (PP) populations were subsets of the ITT populations without protocol violations that could affect treatment efficacy. The ITT population was the primary population for evaluation of efficacy. Safety was evaluated in the ITT population.</p> <p>The principal efficacy analysis for all primary and secondary efficacy variables involved calculating a point estimate and associated 2-sided 95% confidence interval (CI) incorporating a continuity correction of one half. The robustness of the primary analysis was assessed using the same analysis method on the primary efficacy variable for subjects in the Bacteriology PP population and also on the observed cases only for subjects in the Bacteriological ITT population.</p>	
<p>Study Population: Male and female subjects, aged at least 16 years, with a clinical and radiological diagnosis of CAP based on chest X-ray criteria and a number of specific signs and symptoms as defined in the protocol. The protocol was amended on 3 August 2000 to include only subjects with a positive urine test for pneumococcal antigen at screening and/or with the confirmed presence of Gram-positive diplococci suggesting the presence of <i>S. pneumoniae</i>, on direct examination of a Gram-stained sputum/invasive respiratory sample smear. A later protocol amendment (27 June 2001) changed the primary objective to particularly evaluate the treatment of CAP in subjects with an infection due to PRSP with an amoxicillin ± clavulanic acid MIC of $\geq 4\mu\text{g/mL}$. Subjects with conditions or receiving medications that might interfere with the efficacy assessments were excluded from the study. Subjects who had conditions which might compromise safety or tolerability, or who were considered likely to be non-compliant with study procedures were also excluded.</p>	
	Amoxicillin/clavulanate SR 2000/125mg
Number of Subjects:	
Planned, N	1800
Enrolled, N	1903
Treated (Safety Population), N	1900*
ITT Efficacy Population, N	1888*
Completed, n (%)	1578 (83.6)
Total Number Subjects Withdrawn, n (%)	310 (16.4)
Withdrawn due to Adverse Events, n (%)	93 (4.9)
Withdrawn due to Lack of Efficacy, n (%)	63 (3.3)
Withdrawn for Other Reasons, n (%)	154 (8.2)
* 1900 subjects received study treatment; 12 subjects were excluded from all efficacy analyses due to a disqualified investigator.	
Demographics	
N (ITT)	1888
Females: Males	778: 1108
Mean Age, years (SD)	46.5 (18.5)
White, n (%)	1154 (61.1)
Primary Efficacy Results: Bacteriological ITT Population	
	Amoxicillin/clavulanate SR 2000/125mg
Bacteriological response at test of cure:	
Subjects with screening PRSP and amoxicillin/clavulanate MIC $\geq 4\mu\text{g/mL}$	n=10
Success, n (%)	8 (80.0)
Failure, n (%)	2 (20.0)
95% CI for success rate	44.4, 97.5
p-value	Not applicable
Subjects with screening PRSP	n=43
Success, n (%)	35 (81.4)
Failure, n (%)	8 (18.6)
95% CI for success rate	66.6, 91.6
p-value	Not applicable
Subjects with <i>S. pneumoniae</i>	N=394

Success, n (%)	331 (84.0)
Failure, n (%)	63 (16.0)
95% CI for success rate	80.0, 87.5
p-value	Not applicable
All subjects in Bacteriological ITT Population	
	n=665
Success, n (%)	530 (79.7)
Failure, n (%)	135 (20.3)
95% CI for success rate	76.4, 82.7
p-value	Not applicable
Secondary Outcome Variable(s):	
	Amoxicillin/clavulanate SR 2000/125mg
Bacteriological response at end of therapy: Bacteriology ITT population	
	N=665
Success, n (%)	581 (87.4)
Failure, n (%)	84 (12.6)
95% CI for success rate	84.5, 89.7
Subjects with <i>S. pneumoniae</i>	
	N=394
Success, n (%)	360 (91.4)
Failure, n (%)	34 (8.6)
95% CI for success rate	88.1, 93.9
Clinical response at test of cure: Clinical ITT Population	
	N=1888
Success, n (%)	1478 (78.3)
Failure, n (%)	410 (21.7)
95% CI for success rate	76.3, 80.1
Clinical response at end of therapy: Clinical ITT Population	
	N=1888
Success, n (%)	1592 (84.3)
Failure, n (%)	296 (15.7)
95% CI for success rate	82.6, 85.9
Radiological response at test of cure: Clinical ITT Population	
	N=1888
Success, n (%)	1471 (77.9)
Failure, n (%)	62 (3.3)
Unable to determine, n (%)	355 (18.8)
95% CI for success rate	76.0, 79.8
Radiological response at end of therapy: Clinical ITT Population	
	N=1888
Success, n (%)	1520 (80.5)
Failure, n (%)	193 (10.2)
Unable to determine, n (%)	175 (9.3)
95% CI for success rate	78.6, 82.3
Safety Results (Safety Population): Adverse events (AEs) and serious adverse events (SAEs) were recorded on-therapy (any time after the screening visit up to and including the last day of study medication) until Visit 4 (Day 28-35). AEs and SAEs were summarized as on-therapy plus 30 days post-therapy.	
	Amoxicillin/clavulanate SR 2000/125mg (N=1900)
Most Frequent Adverse Events – On-Therapy plus 30 Days Post-Therapy	
	n (%)
Subjects with any AE(s), n (%)	982 (51.7)
Diarrhea	272 (14.3)
Headache	87 (4.6)
Nausea	62 (3.3)

Insomnia	54 (2.8)
Vomiting	51 (2.7)
Alanine aminotransferase increased	48 (2.5)
Pneumonia	48 (2.5)
Abdominal pain	26 (1.4)
Constipation	24 (1.3)
Aspartate aminotransferase increased	22 (1.2)
Dizziness	22 (1.2)
Platelet count increased	22 (1.2)
Serious Adverse Events (SAEs) - On-Therapy plus 30 Days Post-Therapy n (%) [n considered by the investigator to be related to study medication]	
	Amoxicillin/clavulanate SR 2000/125mg (N=1900)
Subjects with fatal and non-fatal SAEs, n (%)	112 (5.9)
	n (%) [related]
Pneumonia	34 (1.8) [8]
Empyema	5 (0.3) [0]
Lung neoplasm malignant	5 (0.3) [0]
Cardiac failure congestive	4 (0.2) [0]
Drug ineffective	4 (0.2) [0]
Pyrexia	4 (0.2) [0]
Pleural effusion	3 (0.2) [0]
Pulmonary embolism	3 (0.2) [0]
Bronchial carcinoma	2 (0.1) [0]
Cardiac arrest	2 (0.1) [0]
Chronic obstructive airway disease exacerbated	2 (0.1) [0]
Pleurisy	2 (0.1) [0]
Real failure acute	2 (0.1) [0]
Respiratory failure	2 (0.1) [0]
Septic shock	2 (0.1) [0]
Tuberculosis	2 (0.1) [0]
Abdominal pain	1 (0.1) [0]
Accidental overdose	1 (0.1) [1]
Adverse drug reaction	1 (0.1) [0]
Alanine aminotransferase increased	1 (0.1) [0]
Anxiety	1 (0.1) [0]
Arrhythmia supraventricular	1 (0.1) [0]
Arterial stenosis	1 (0.1) [0]
Arthritis	1 (0.1) [0]
Atelectasis	1 (0.1) [0]
Atrial fibrillation	1 (0.1) [0]
B-cell lymphoma	1 (0.1) [0]
Bronchial neoplasm	1 (0.1) [0]
Bronchopneumonia	1 (0.1) [0]
Carcinoid tumour of the gastrointestinal tract	1 (0.1) [0]
Cardiac disorder	1 (0.1) [0]
Cardiac failure	1 (0.1) [0]
Cardiac failure acute	1 (0.1) [0]
Cardio-respiratory arrest	1 (0.1) [0]
Cardiomegaly	1 (0.1) [0]
Cardiomyopathy	1 (0.1) [0]
Cerebrovascular accident	1 (0.1) [0]
Chest injury	1 (0.1) [0]
Cholelithiasis	1 (0.1) [0]

Congestive cardiomyopathy	1 (0.1) [0]
Contrast media reaction	1 (0.1) [0]
Death	1 (0.1) [0]
Deep vein thrombosis	1 (0.1) [0]
Diarrhea	1 (0.1) [1]
Dizziness	1 (0.1) [0]
Dyspepsia	1 (0.1) [0]
Dyspnea exacerbated	1 (0.1) [0]
Encephalitis	1 (0.1) [0]
Epistaxis	1 (0.1) [0]
Gastritis erosive	1 (0.1) [0]
Headache	1 (0.1) [0]
Henoch-Schonlein purpura	1 (0.1) [0]
Hypertension	1 (0.1) [0]
Hyperthermia	1 (0.1) [0]
Hypoglycemia	1 (0.1) [0]
Hypotension	1 (0.1) [0]
Hypoxia	1 (0.1) [0]
Increased bronchial secretion	1 (0.1) [0]
Intestinal adenocarcinoma	1 (0.1) [0]
Joint injury	1 (0.1) [0]
Liver abscess	1 (0.1) [0]
Lower respiratory tract infection	1 (0.1) [0]
Lung abscess	1 (0.1) [0]
Lung adenocarcinoma	1 (0.1) [0]
Lung disorder	1 (0.1) [0]
Lung squamous cell carcinoma stage unspecified	1 (0.1) [0]
Myocardial infarction	1 (0.1) [0]
Nasopharyngeal cancer	1 (0.1) [0]
Obesity	1 (0.1) [0]
Pneumocystis carinii pneumonia	1 (0.1) [0]
Pneumomediastinum	1 (0.1) [0]
Pneumonia hemophilus	1 (0.1) [0]
Pneumonia legionella	1 (0.1) [0]
Pneumonia necrotizing	1 (0.1) [0]
Pneumonia primary atypical	1 (0.1) [0]
Pneumothorax	1 (0.1) [0]
Pulmonary congestion	1 (0.1) [0]
Pulmonary granuloma	1 (0.1) [0]
Pulmonary tuberculosis	1 (0.1) [0]
Renal insufficiency	1 (0.1) [0]
Respiratory distress	1 (0.1) [1]
Sudden death	1 (0.1) [0]
Teratoma	1 (0.1) [0]
Toxic shock syndrome	1 (0.1) [0]
Typhoid fever	1 (0.1) [0]
Viral myocarditis	1 (0.1) [0]
Subjects with fatal SAEs, n (%)	24 (1.3)
	n (%) [related]
Pulmonary embolism	3 (0.2) [0]
Cardiac failure congestive	2 (0.1) [0]
Lung neoplasm malignant	2 (0.1) [0]
Bronchial neoplasm	1 (0.1) [0]
Bronchopneumonia	1 (0.1) [0]

Cardiac arrest	1 (0.1) [0]
Cardiac failure acute	1 (0.1) [0]
Cardiomegaly	1 (0.1) [0]
Cardio-respiratory arrest	1 (0.1) [0]
Cerebrovascular accident	1 (0.1) [0]
Death (unknown cause)	1 (0.1) [0]
Lung adenocarcinoma	1 (0.1) [0]
Myocardial infarction	1 (0.1) [0]
Pneumocystis carinii pneumonia	1 (0.1) [0]
Pneumonia	1 (0.1) [0]
Pulmonary congestion	1 (0.1) [0]
Renal failure	1 (0.1) [0]
Sudden death	1 (0.1) [0]
Tuberculosis	1 (0.1) [0]
Viral myocarditis	1 (0.1) [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.

Bhatt K, Kalia V, Berkowitz E, Twynholm M, Abraham-van Parijs B, Hodge R. Efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg (PKE AMX/CA) in patients with community-acquired pneumonia (CAP), including cases caused by penicillin-resistant *S. pneumoniae*. Abstracts from the 15th European Congress of Clinical Microbiology and Infectious Diseases, April 2005.

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.

Thomas M, File T, Jacobs MR, Poole MD, Wynne B. 2002. Outcome of treatment of respiratory tract infections due to *Streptococcus pneumoniae*, including drug-resistant strains, with pharmacokinetically enhanced amoxicillin/clavulanate. *Int J Antimicrob Agents* 20(4):235-47.

Garau J. 2004. Performance in practice: bacteriological efficacy in patients with drug-resistant *S. pneumoniae*. *Clin*

Microbiol Infect. 10(suppl. 2): 28-35.

File T, Garau J, Jacobs MR, Wynne B. 2003. Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg in the treatment of community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae*, including penicillin-resistant strains. 41st Annual Meeting of the Infectious Disease Society of America, San Francisco, USA. Abstract 303.

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