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Study No.: 550
Title: A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral <i>Augmentin</i> SR, Two Tablets Equal to 2000/125mg, Twice Daily for 10 Days Versus Levofloxacin (Levaquin) 500mg Once Daily for 10 Days in the Treatment of Adults with Acute Bacterial Sinusitis Infections.
Rationale: The purpose of this study was to demonstrate that oral Augmentin SR tablets (pharmacokinetically enhanced amoxicillin/clavulanate) 2000/125mg twice daily (bid) for 10 days is at least as good as oral levofloxacin 500mg once daily (od) for 10 days in the treatment of acute bacterial sinusitis (ABS).
Phase: III
Study Period: 15 November 1999 to 14 February 2000.
Study Design: Randomised, double-blind, double-dummy, multicenter, parallel group study. Subjects were instructed to attend the clinic at screening (Visit 1, day 0), on-therapy (Visit 2, day 3-5), end of therapy (Visit 3, day 12-14) and follow up (Visit 4, day 17-24).
Centres: A total of 62 centres in France (19), Germany (14) and US (29). Data from 2 US centres were removed as requested by the Food and Drug Administration (FDA).
Indication: Acute bacterial sinusitis.
Treatment: Subjects were randomized to one of two treatment groups, in a 1:1 ratio Treatment group A: 10 days of oral treatment with amoxicillin/clavulanate SR 2000/125mg bid plus placebo to levofloxacin 500mg od or Treatment group B: 10 days of oral treatment with levofloxacin 500mg od, plus placebo to amoxicillin/clavulanate SR 2000/125mg bid.
Objectives: The primary objective was to demonstrate that the clinical efficacy of amoxicillin/clavulanate 2000/125mg twice daily for 10 days was at least as effective as that of levofloxacin 500mg once daily for 10 days in the treatment of ABS. The secondary objective was to evaluate the bacteriological efficacy and safety of amoxicillin/clavulanate SR 2000/125mg twice daily for 10 days compared with levofloxacin 500 mg once daily for 10 days in patients with ABS.
Primary Outcome/Efficacy Variable: The combined clinical and radiological response (success, failure or unable to determine) at follow up (Visit 4). Clinical success was defined as sufficient resolution of signs and symptoms of ABS such that no additional antibacterial therapy for ABS was indicated. Clinical failure at follow up was defined as reappearance or deterioration of signs and symptoms of ABS following clinical success at end of therapy. If a patient was deemed to be a clinical failure at any visit, this outcome was carried forward to all further visits. Radiological outcome of "improved" was defined as improvement or resolution of radiological signs of ABS. Radiological outcome of "unchanged" was defined as no improvement in the baseline radiological signs of ABS. Radiological outcome of "worse" was defined as a worsening of the baseline radiological signs of ABS, or the appearance of new radiological signs of ABS. "Unable to determine" was defined as a valid assessment of radiological outcome could not be made. Combined clinical and radiological response at follow up was defined as success when there was a clinical outcome of success and the radiological outcome was improved or unchanged. Combined clinical and radiological response at follow up was defined as failure when there was a clinical outcome of failure at end of therapy, or clinical outcome at follow up was recurrence, and/or a radiological outcome was worse at follow up. Combined clinical and radiological response at follow up was defined as unable to determine when either the patient's clinical outcome at end of therapy or follow up was unable to determine and radiological outcome at follow up was improved, unchanged, unable to determine, or unknown; or the clinical response at follow up was success and the radiological outcome was unable to determine or unknown.
Secondary Outcome/Efficacy Variable(s): Clinical response (success or failure) at follow up (Visit 4) Clinical response (success or failure) at end of therapy (Visit 3). Bacteriological response (success or failure) at follow up (Visit 4). 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 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 stage, this outcome was carried forward to all further visits		
<p>Statistical Methods: Four subject populations were defined for the analysis of clinical and bacteriological efficacy: intent-to-treat (ITT) included all randomised subjects who took at least one dose of study medication; clinical per-protocol (PP), a subset of ITT that excluded subjects who violated any aspect of the protocol to an extent that may affect treatment efficacy; bacteriology ITT included all randomised subjects who took at least one dose of study medication and had at least one typical pre-therapy pathogen identified at screening; bacteriology PP, a subset of the bacteriology ITT that excluded subjects who violated any aspect of the protocol to an extent that may affect treatment efficacy. The safety population was the same as the ITT population.</p> <p>The primary efficacy analysis was based on an unstratified comparison of clinical and radiological 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 potassium was drawn if the lower limit of the CI (amoxicillin/clavulanate potassium minus levofloxacin) was $\geq -15\%$.</p>		
<p>Study Population: Subjects of either gender and at least 18 years of age who presented with signs and symptoms of ABS of at least 7 but less than 28 days duration (defined by purulent nasal discharge or purulence in the nasal cavity and at least one major or two minor specified criteria of ABS). Subjects were to have radiological confirmation of ABS. Subjects with a history of chronic sinusitis, intraorbital or intracranial complications that would have interfered with the interpretation of the radiological images, concomitant infection, or treatment with antibiotics within seven days were excluded.</p>		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Levofloxacin 500mg od
Number of Subjects:		
Planned, N	400	
Randomised, N	179	184
Treated (ITT/Safety Population), N	178	182
Clinical PP Population at Follow Up	123	140
Completed, n (%)	163 (91.6)	177 (97.3)
Total Number Subjects Withdrawn, n (%)	15 (8.4)	5 (2.7)
Withdrawn due to Adverse Events, n (%)	5 (2.8)	1 (0.5)
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for Other Reasons, n (%)	10 (5.6)	4 (2.2)
Demographics	Amoxicillin / clavulanate SR 2000 / 125mg bid	Levofloxacin 500mg od
N (ITT)	178	182
Females: Males	109: 69	106: 76
Mean Age, years (SD)	41.0 (13.6)	40.1 (13.4)
White, n (%)	166 (93.3)	157 (86.3)
Primary Efficacy Results: Clinical PP Population		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=123)	Levofloxacin 500mg od (N=140)
Combined Clinical and Radiological Response at Follow Up		
Success, n (%)	103 (83.7)	118 (84.3)
Failure, n (%)	18 (14.6)	20 (14.3)
Unable to Determine, n (%)	2 (1.6)	2 (1.4)
Treatment Difference % (Amox/clav SR – Levoflox)	-0.5	
95% CI	-9.4, 8.3	
p-value	Not applicable	
Secondary Outcome Variable(s):		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	Levofloxacin 500mg od
Clinical Response at Follow Up: Clinical PP Population		
	N=123	N=140
Success, n (%)	107 (87.0)	124 (88.6)
Failure, n (%)	16 (13.0)	16 (11.4)

Treatment Difference % (Amox/clav SR – Levoflox)	-1.6	
95% CI	-9.5, 6.4	
Clinical Response at End of Therapy: Clinical PP Population		
	N=129	N=145
Success, n (%)	121 (93.8)	139 (95.9)
Failure, n (%)	8 (6.2)	6 (4.1)
Treatment Difference % (Amox/clav SR – Levoflox)	-2.1	
95% CI	-7.3, 3.2	
Bacteriological Response at Follow Up: Bacteriology PP Population		
	N=15	N=10
Success, n (%)	14 (93.3)	10 (100)
Failure, n (%)	1 (6.7)	0
Bacteriological Response at End of Therapy: Bacteriology PP Population		
	N=15	N=11
Success, n (%)	15 (100)	11 (100)
Failure, n (%)	0	0
Safety Results: Safety Population -Safety Results: Safety Population - An on-therapy adverse event (AE) was defined as an AE which started at any time from the date of the screening visit up to and including the last day of study medication. AEs were summarised that occurred on-therapy and up to and including 30 days after the last day of study medication.		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=178)	Levofloxacin 500mg od (N=182)
Most Frequent Adverse Events – On-Therapy Plus 30 Days Post-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	103 (57.9)	82 (45.1)
Diarrhoea	51 (28.7)	13 (7.1)
Nausea	11 (6.2)	12 (6.6)
Moniliasis genital	9 (5.1)	2 (1.1)
Abdominal pain	6 (3.4)	4 (2.2)
Dyspepsia	5 (2.8)	1 (0.5)
Insomnia	4 (2.2)	2 (1.1)
Creatine phosphokinase increased	3 (1.7)	2 (1.1)
Fatigue	3 (1.7)	2 (1.1)
Rash	3 (1.7)	0
Back pain	2 (1.1)	4 (2.2)
Conjunctivitis	2 (1.1)	1 (0.5)
Hepatic enzymes increased	2 (1.1)	0
Infection fungal	2 (1.1)	2 (1.1)
Migraine	2 (1.1)	0
Otitis media	2 (1.1)	1 (0.5)
Pruritus	2 (1.1)	2 (1.1)
Rhinitis	2 (1.1)	2 (1.1)
Rigors	2 (1.1)	0
Taste perversion	2 (1.1)	1 (0.5)
Upper respiratory tract infection	2 (1.1)	1 (0.5)
Vaginitis	2 (1.1)	2 (1.1)
Vomiting	2 (1.1)	1 (0.5)
Asthma	1 (0.6)	2 (1.1)
Epistaxis	1 (0.6)	2 (1.1)
Headache	1 (0.6)	4 (2.2)
Herpes simplex	1 (0.6)	2 (1.1)
Infection viral	1 (0.6)	3 (1.6)
Injury	1 (0.6)	6 (3.3)
Pharyngitis	1 (0.6)	3 (1.6)

Mouth dry	0	3 (1.6)
Dysuria	0	2 (1.1)
Ear disorder, not otherwise specified	0	2 (1.1)
Gastroenteritis	0	2 (1.1)
Pain	0	2 (1.1)
Paroniria	0	2 (1.1)
Purpura	0	2 (1.1)
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 bid (N=178)	Levofloxacin 500mg od (N=182)
Subjects with non-fatal SAEs, n (%)	1 (0.6)	0
	n (%) [related]	n (%) [related]
Colitis	1 (0.6) [1]	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

See publications below.

Publications:

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.

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.

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