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Study No.: 536
Title: An Open-Label Study to Demonstrate Bacteriological Efficacy of <i>Augmentin</i> ES in the Treatment of Acute Otitis Media Due to <i>S. pneumoniae</i> .
Rationale: <i>Streptococcus pneumoniae</i> is the most common bacterial cause of acute otitis media (AOM), as well as the least likely to spontaneously resolve. Drug-resistant <i>S. pneumoniae</i> (DRSP) is a well established cause of AOM in many regions of Europe and is increasingly a cause of AOM in children in the US. Therapeutic choices in treating outpatient infections caused by DRSP are limited, and treatment failures have been reported. In cases of suspected DRSP, clinicians are recommending the use of higher doses of amoxicillin. An extra strength (ES) amoxicillin/clavulanate potassium formulation (14:1) has been developed to treat AOM in cases where DRSP is suspected with the clavulanate component providing coverage for beta-lactamase producing strains of other common pathogens in AOM.
Phase: IIIB
Study Period: 24 February 1999 to 12 June 2000.
Study Design: Open-label, non-comparative study in children with AOM. Patients were expected to attend the clinic four times over a duration of approximately four weeks: a preliminary visit (Visit 1, Day 1), on-therapy (Visit 2, Day 4-6), end-of-treatment (Visit 3, Day 12-15) and follow-up (Visit 4, Day 25-28). Patients with an intact eardrum had a tympanocentesis (puncture of the eardrum) procedure performed at the preliminary visit to obtain specimens of middle ear fluid for bacteriological evaluation. (Patients with ruptured eardrum and purulent discharge of less than 24 hours provided a sample directly for evaluation.) <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Streptococcus pyogenes</i> , & <i>Staphylococcus aureus</i> species were considered pathogens. Patients from whom <i>S. pneumoniae</i> was isolated (either alone or in combination with other pathogens) had a repeat tympanocentesis at the on-therapy visit. Patients from whom only other pathogens were isolated at the preliminary visit had a second tympanocentesis performed either in instances of clinical failure, or alternatively, performed on all patients.
Centres: The study was conducted at 25 sites in 5 countries (Costa Rica [1], Dominican Republic [1], Guatemala [1], Israel [1] and the United States [21]).
Indication: Acute otitis media.
Treatment: Patients received 10 days of treatment with the volume of reconstituted study medication equaling 90/6.4mg/kg/day of amoxicillin/clavulanate potassium ES.
Objectives: The primary objective was to assess the bacteriological activity of amoxicillin/clavulanate ES in divided doses every 12 hours in children with AOM due to <i>S. pneumoniae</i> with an amoxicillin/clavulanic acid minimum inhibitory concentration (MIC) of 4.0mcg/mL. The secondary objectives included assessment of the clinical and bacteriological efficacy of amoxicillin/clavulanate ES in patients with AOM due to any pathogen, demonstration of the clinical efficacy of amoxicillin/clavulanate ES in patients infected with <i>S. pneumoniae</i> with an amoxicillin/clavulanic acid MIC of 4.0mcg/mL, and determination of the incidence of adverse experiences (AEs), in particular diarrhea, in patients receiving amoxicillin/clavulanate ES 90/6.4mg/kg/day in divided doses every 12 hours.
Primary Outcome/Efficacy Variable: Bacteriological response (success or failure) in patients with AOM due to <i>S. pneumoniae</i> with an amoxicillin/clavulanic acid MIC of 4.0mcg/mL at the on-therapy visit (Day 4-6). Success was defined as eradication of <i>S. pneumoniae</i> , or no middle ear fluid present. Failure was defined as persistence of <i>S. pneumoniae</i> , or if bacteriological evaluation could not be made. Response was based solely on results of the second tympanocentesis at Day 4-6; no results were imputed from clinical response at the end-of-treatment (Day 12-15) visit.
Secondary Outcome/Efficacy Variable(s): Bacteriological response (success or failure) of <i>S. pneumoniae</i> (alone or with other pathogens) to study medication at the on-therapy visit (Day 4-6). Success was defined as eradication of <i>S. pneumoniae</i> , or no middle ear fluid present. Failure was defined as persistence of <i>S. pneumoniae</i> , or if bacteriological evaluation could not be made. Response was based solely on results of the second tympanocentesis at Day 4-6; no results were imputed from clinical response at the end-of-treatment (Day 12-15) visit. Bacteriological response (success or failure) of other pathogens to study medication at the on-therapy visit (Day 4-6). Success was defined as eradication of the pathogen, or no middle ear fluid present. Failure was defined as persistence of the pathogen, or if bacteriological evaluation could not be made. Response was based solely on results of the second tympanocentesis at Day 4-6; no results were imputed from clinical response at the end-of-treatment (Day 12-15) visit.

<p>Bacteriological response of other pathogens to study medication at the end-of-treatment visit (Day 12-15). 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 (presumed bacteriological eradication). 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> <p>Clinical response (success or failure) at the end-of-treatment visit (Day 12-15) in patients with AOM due to <i>S. pneumoniae</i> with an amoxicillin/clavulanic acid MIC of 4.0mcg/mL.</p> <p>Clinical response (success or failure) at the end-of-treatment visit (Day 12-15).</p> <p>Clinical response (success or failure) at the follow-up visit (Day 25-28).</p> <p>Clinical success was defined as sufficient resolution of AOM such that no additional antibacterial therapy for AOM was indicated. Clinical failure was recorded when there was insufficient improvement of AOM at the end-of-treatment visit requiring additional antibacterial therapy. Clinical failure at follow-up was defined as reappearance or deterioration of AOM following clinical success at the end-of-treatment visit. If a patient was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits.</p> <p>Protocol defined diarrhea (PDD) was defined as three or more watery stools in one day or two or more watery stools per day for two consecutive days during Days 1-11, as recorded in patient diaries. Additionally, any event of diarrhea noted by the investigator as an adverse event was included as a PDD event in this analysis, even if not recorded in patient diaries.</p>	
<p>Statistical Methods: The safety population included all patients who took at least one dose of study medication; the clinical PP population included subjects with a clinical diagnosis of AOM as defined in the protocol, who received 80% to 120% of study medication while on therapy and took no prohibited medication, and who received at least three full days (6 doses) of study medication; and the bacteriological PP population included patients who received at least three full days (6 doses) of study medication, met the entry criteria and had a baseline middle ear fluid (MEF) culture positive for <i>S. pneumoniae</i> alone or with other pathogens. The on-therapy bacteriological response, end-of-treatment presumptive bacteriological response, and end-of-treatment and test-of-cure clinical responses were tabulated using descriptive statistics.</p>	
<p>Study Population: Subjects of either gender, between the ages of 3 to 48 months, with protocol-defined otitis media, diagnosed on the basis of otoscopic findings, as defined below: purulent otorrhea of less than 24 hours duration, or middle ear effusion (MEE) plus acute inflammation Subjects weighing more than 40 kg or who had spontaneous perforation of the tympanic membrane and drainage for longer than 24 hours were excluded, as were subjects with tympanostomy tubes in place.</p>	
	Amoxicillin / clavulanate ES
Number of Subjects:	
Planned, N	700
Safety Population, N	663
Clinical Per-Protocol (PP) Population (with <i>S.pneumoniae</i> alone or with other pathogens) at end of therapy	171
Bacterial Per-Protocol (PP) Population (with <i>S.pneumoniae</i> alone or with other pathogens) at On-Therapy Visit	154
Completed, n (% of Safety Population)	390 (58.8)
Total Number Subjects Withdrawn, n (%)	273 (41.2)
Withdrawn due to Adverse Events n (%)	35 (5.3)
Withdrawn due to Lack of Efficacy n (%)	6 (0.9)
Withdrawn for Other Reasons, n (%)	232 (35.0)
	Amoxicillin / clavulanate ES
Demographics	
N (ITT)	663
Females: Males	266:397
Mean Age, months (SD)	17.9 (11.7)
Caucasian n (%)	406 (61.2)
Primary Efficacy Results: Bacteriology PP with <i>S. pneumoniae</i> and amox/clav MIC = 4.0 mcg/mL Population	
	Amoxicillin / clavulanate ES (n=4)

Bacteriological Response at On-Therapy Visit	
Success, n (%)	4 (100)
Failure, n (%)	0
Treatment Difference %	Not applicable
95% CI	Not applicable
p-value	Not applicable
Secondary Outcome Variable(s):	
	Amoxicillin / clavulanate ES
Bacteriological Response at On-Therapy Visit: Bacteriology PP with <i>S. pneumoniae</i> Population	
	n=154
Success, n (%)	150 (97.4)
Failure, n (%)	4 (2.6)
Bacteriological Response at On-Therapy Visit: Bacteriology PP with Other Pathogens Population	
	n=178
Success, n (%)	167 (93.8)
Failure, n (%)	11 (6.2)
Presumed Bacteriological Response at End-of-Treatment: Bacteriology PP with Other Pathogens Population	
	n=116
Success, n (%)	102 (87.9)
Failure, n (%)	14 (12.1)
Clinical Response at End-of-Treatment: Clinical PP population	
<i>S. pneumoniae</i>	n=171
Success, n (%)	154 (90.1)
Failure, n (%)	17 (9.9)
<i>S. pneumoniae</i> with amox/clav MIC = 2 mcg/mL	n=25
Success, n (%)	21 (84.0)
Failure, n (%)	4 (16.0)
<i>S. pneumoniae</i> with amox/clav MIC = 4 mcg/mL	n=4
Success, n (%)	4 (100)
Failure, n (%)	0
<i>S. pneumoniae</i> with amox/clav MIC = 8 mcg/mL	n=7
Success, n (%)	5 (71.4)
Failure, n (%)	2 (28.6)
<i>H. influenzae</i>	n=210
Success, n (%)	185 (88.1)
Failure, n (%)	25 (11.9)
<i>M. catarrhalis</i>	n=36
Success, n (%)	31 (86.1)
Failure, n (%)	5 (13.9)
<i>S. pyogenes</i>	n=17
Success, n (%)	16 (94.1)
Failure, n (%)	1 (5.9)
<i>S. aureus</i>	n=15
Success, n (%)	13 (86.7)
Failure, n (%)	2 (13.3)
Clinical Response at Follow Up: Clinical PP Population	
<i>S. pneumoniae</i>	n=169
Success, n (%)	125 (74.0)
Failure, n (%)	44 (26.0)
<i>H. influenzae</i>	n=203
Success, n (%)	140 (69.0)
Failure, n (%)	63 (31.0)
<i>M. catarrhalis</i>	n=35
Success, n (%)	22 (62.9)
Failure, n (%)	13 (37.1)

<i>S. aureus</i>	n=15
Success, n (%)	10 (66.7)
Failure, n (%)	5 (33.3)
<i>S. pyogenes</i>	n=18
Success, n (%)	15 (83.3)
Failure, n (%)	3 (16.7)
Safety Results: Safety Population –Safety Results - Adverse events (AE) were recorded after administration of the first dose of study medication up to the final visit. Serious adverse events (SAEs) were recorded during the clinical study or within 30 days of receiving the last dose of study medication.	
	Amoxicillin/clavulanate potassium ES (N=663)
Most Frequent Adverse Events – On-Therapy or At Any Time During the Study	n (%)
Subjects with any AE(s), n(%)	266 (40.1)
Fever	57 (8.6)
Vomiting	48 (7.2)
Contact dermatitis	44 (6.6)
Diarrhea	33 (5.0)
Upper respiratory tract infection	28 (4.2)
Otitis media	27 (4.1)
Rhinitis	23 (3.5)
Earache	18 (2.7)
Rash	17 (2.6)
Coughing	15 (2.3)
Moniliasis	15 (2.3)
Protocol-defined diarrhea was reported for 81 patients (12.2%).	
Serious Adverse Events (SAEs)- On-Therapy or At Any Time During the Study n (%) [n considered by the investigator to be related to study medication]	
	Amoxicillin/clavulanate potassium ES (N=663)
	n (%) [related]
Subjects with non-fatal SAEs, n (%)	12 (1.8) [3]
Therapeutic response increased	3 (0.5) [1]
Injury	2 (0.3) [0]
Diarrhea	2 (0.3) [2]
Vomiting	1 (0.2) [0]
Pneumonia	2 (0.3) [0]
Asthma	1 (0.2) [0]
Dehydration	1 (0.2) [1]
Otitis media	1 (0.2) [0]
	n (%) [related]
Subjects with fatal SAEs, n (%)	0

Conclusion:

See publications below.

Publications:

Dagan R, Hoberman A, Johnson C, Leibovitz EL, Arguedas A, Rose FV, Wynne BR, Jacobs MR. Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. *Pediatr Infect Dis J* 2001; 20(9): 829–837.

Dagan R, Hoberman A, Leibovitz E, Arguedas A, Wynne B, Rose FV, Jacobs M. Bacteriological and clinical efficacy of a new amoxicillin/clavulanate extra-strength formulation (A/C 14:1) in the treatment of acute otitis media. Abstracts from the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy 2000; Abstract 107, p 491.

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