

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 447
Title: A Comparison of the Safety and Efficacy of q 12 hrs <i>Augmentin</i> -90/6.4 mg/kg/day and q 12 hrs <i>Augmentin</i> -45/6.4 mg/kg/day in the Treatment of Acute Otitis Media in Children: A Randomized Double-Blind, Multicenter, Comparative Study.
Rationale: The increase in pneumococcal minimum inhibitory concentrations (MICs) seen in the in the past 5 to 10 years are likely to continue and empiric therapy of drug-resistant <i>Streptococcus pneumoniae</i> (DRSP) infections may require the availability of a high dose amoxicillin regimen. A study to specifically establish clinical/bacteriological outcomes is not feasible because subjects with <i>S. pneumoniae</i> with amoxicillin MICs ≥ 2 mcg/mL are currently difficult to obtain in large numbers. However, efficacy can be predicted from pharmacodynamic arguments. To establish the tolerance of such a regimen, this study compared the efficacy and incidence of adverse experiences (AEs), particularly protocol-defined diarrhea (PDD), in subjects receiving amoxicillin/clavulanate potassium 90/6.4 mg/kg/day or amoxicillin/clavulanate potassium 45/6.4 mg/kg/day.
Phase: III
Study Period: 11 December 1996 to 28 February 1997.
Study Design: A prospective, randomized, double-blind, multicenter, comparative, active controlled study. Subjects made three clinic visits: screening (day 0), end of therapy (EOT) (Days 12 to 14) and follow-up (FU) (Days 22 to 28).
Centers: 19 centers in the USA.
Indication: Acute otitis media (AOM).
Treatment: Subjects were randomized to one of two treatment groups in a 1:1 ratio: Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day administered in two divided doses every 12 hours (q 12 hours) with food for 10 days or Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day administered in two divided doses q 12 hours with food for 10 days.
Objectives: The primary objective was to compare the incidence of AEs, particularly lower gastrointestinal disturbances that satisfied the criteria of PDD, in children with AOM treated with Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day or Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day, each administered in two divided doses every 12 hrs with food for 10 days. The secondary objective was to compare the clinical efficacy of Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day and Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day at EOT in the treatment of AOM in children.
Primary Safety Variable: The incidence of PDD, defined as three or more watery stools in one day (1 day of PDD) or two watery stools per day for two consecutive days (2 days of PDD), was collected from patient diary cards during therapy, and was calculated and compared across treatment groups.
Primary Outcome/Efficacy Variable: Clinical response (success or failure) at EOT. Clinical success at EOT 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 EOT requiring additional antibacterial therapy.
Secondary Outcome/Efficacy Variable(s): Recurrence at FU for patients who were considered treatment successes at EOT and global clinical response (success or failure) based on clinical outcomes at EOT and FU. Clinical success at EOT was defined as sufficient resolution of AOM such that no additional antibacterial therapy for AOM was indicated. Clinical failure at follow up (FU) was defined as reappearance or deterioration of AOM following clinical success at EOT.
Statistical Methods: The Intent-to-Treat (ITT) population included all randomized subjects who took at least one dose of study medication. Safety was evaluated in the ITT population. The ITT Bowel Habit population contained those subjects for whom bowel habit data were available. The Per-Protocol (PP) population contained those subjects without protocol violations that would bias the clinical efficacy assessment. The PP population was the primary population for evaluation of efficacy. Two-sided 95% confidence intervals (CIs) were used to indicate the range of differences between treatments. All treatment differences refer to the difference of Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day minus Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day. Assuming an underlying equivalent PDD response rate of 10%, a sample size of 380 subjects (190 per treatment arm) was required to give a 90% power to detect that the upper bound of the two-sided 95% confidence interval for the difference in rates (Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day minus Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day) was no more than 10%.
Study Population: Male or female subjects aged 3 months to 12 years, able to comply with the protocol and with a diagnosis of AOM on the basis of otoscopic findings as defined below: a) Purulent otorrhea of less than 24 hrs duration, or

b)	Middle ear effusion as evidenced by at least two of the following:	
	1) decreased or absent tympanic mobility measured by pneumatic otoscopy	
	2) yellow or white discoloration of the tympanic membrane	
	3) opacification of the tympanic membrane	
plus	Acute inflammation as evidenced by at least one of the following:	
	1) ear pain within 24 hrs, including unaccustomed tugging or rubbing of ear	
	2) marked redness of the tympanic membrane	
	distinct fullness or bulging of the tympanic membrane.	
	Subjects weighing more than 40 kg or who had spontaneous perforation of the tympanic membrane and drainage for longer than 24 hours were excluded from the study. Subjects with concomitant antibiotics within one week prior to initiation of the study or with concomitant infection were also excluded.	
	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day
Number of Subjects:		
Planned, N	190	190
Randomized, N	223	230
ITT/Safety Population, N	222	228
ITT Bowel Habit Population, N	218	222
PP EOT Population, N	183	186
Completed, n (% of Safety Population)	197 (88.7)	207 (90.8)
Total Number Subjects Withdrawn, n (%)	25 (11.2)	21 (9.1)
Withdrawn due to Adverse Events, n (%)	7 (3.2)	4 (1.8)
Withdrawn due to Lack of Efficacy, n (%)	4 (1.8)	3 (1.3)
Withdrawn for Other Reasons, n (%)	14 (6.3)	14 (6.1)
Demographics	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day
N (ITT)	222	228
Females: Males	105: 117	100: 128
Mean Age, years (SD)	3.23 (2.59)	3.28 (2.50)
White, n (%)	160 (72.1)	170 (74.6)
Age group, n (%)		
≤6 months	6 (2.7)	14 (6.1)
>6 months and < 2 years	87 (39.2)	80 (35.1)
≥2 years and < 5 years	78 (35.1)	83 (36.4)
≥5 years and <8 years	33 (14.9)	39 (17.1)
≥8 years	18 (8.1)	12 (5.3)
Primary Efficacy Results: (Clinical PP Population)		
Clinical response at end of therapy	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day
	N=183	N=186
Success, n (%)	154 (84.2)	163 (87.6)
Failure, n (%)	29 (15.8)	23 (12.4)
Treatment difference (Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day minus Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day)	-3.5	
95% CI	-10.6, 3.6	
Secondary Outcome Variable(s):		
(Clinical PP population who were 'successes' at end of therapy)	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day
Recurrence at follow-up	N=148	N=154
Yes, n (%)	21 (14.2)	32 (20.8)

No, n (%)	127 (85.8)	122 (79.2)
Treatment difference (Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day minus Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day)	-6.6	
95% CI	-15.1, 1.9	
Global clinical response: (Clinical PP Population)	N=177	N=177
Success, n (%)	127 (71.8)	122 (68.9)
Failure, n (%)	50 (28.2)	55 (31.1)
Treatment difference (Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day minus Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day)	2.8	
95% CI	-6.7, 12.3	
Primary Safety Results		
Subjects with PDD (ITT Bowel Habit Population)	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day
	N=218	N=222
No, n (%)	195 (89.5)	202 (91.0)
Yes, n (%)	23 (10.6)	20 (9.0)
Treatment difference (Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day minus Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day)	1.5	
95% CI	-4.0, 7.1	
Safety Results (ITT population): Treatment-emergent AEs which occurred on-therapy to 30 days post-therapy were recorded.		
	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day (N=222)	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day (N=228)
Most Frequent Adverse Events – On-Therapy until 30 days post-therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	108 (48.6)	105 (46.1)
Coughing	25 (11.3)	15 (6.6)
Vomiting	13 (5.9)	16 (7.0)
Contact dermatitis	13 (5.9)	11 (4.8)
Fever	11 (5.0)	8 (3.5)
Upper respiratory tract infection (URI)	8 (3.6)	21 (9.2)
Rhinitis	8 (3.6)	9 (3.9)
Abdominal pain	8 (3.6)	4 (1.8)
Rash	7 (3.2)	6 (2.6)
Infection fungal	7 (3.2)	4 (1.8)
Pharyngitis	7 (3.2)	3 (1.3)
Infection viral	7 (3.2)	2 (0.9)
Sinusitis	0	4 (1.8)
Serious Adverse Events - On-Therapy until 30 days post-therapy n (%) [n considered by the investigator to be related to study medication] Serious adverse experiences (SAEs) which occurred during the study or within 30 days of receiving study medication, whether or not related to study medication, were recorded.		
	Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day (N=222)	Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day (N=228)
	n (%) [related]	n (%) [related]

Subjects with non-fatal SAEs, n (%)	1 (<1) [0]	0
Accidental overdose	1 (<1) [0]	0
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day administered in divided doses every 12 hours for 10 days was shown to be as effective as amoxicillin/clavulanate potassium 45/6.4 mg/kg/day administered in divided doses every 12 hours for 10 days in the treatment of AOM in children. The incidence of PDD associated with Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day is no higher than that associated with Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day. This study showed no significant difference between Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day and Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day treatment groups in terms of clinical response at the end of therapy. In the Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day group, 108 subjects reported AEs with the most frequently reported AEs being coughing, vomiting, and contact dermatitis. In the Amoxicillin/clavulanate potassium 45/6.4 mg/kg/day group, 105 subjects reported AEs with the most frequently reported AEs being URI, vomiting, and coughing. One SAE, accidental overdose, was reported in the Amoxicillin/clavulanate potassium 90/6.4 mg/kg/day group. There were no fatalities reported during the study.

Publications:

Safety and tolerability of a new formulation (90 mg/kg/day divided every 12 h) of amoxicillin/clavulanate (augmentin) in the empiric treatment of pediatric acute otitis media caused by drug-resistant streptococcus pneumoniae. Bottenfield, G. W., Burch, D. J., Hedrick, J. A., Schaten, R., Rowinski, C. A., and Davies, J. T. *Pediatr Infect Dis J* 98; 17(10):963-8

CLINICAL PROFILE OF A NEW FORMULATION OF AMOXICILLIN/CLAVULANATE (A/C) FOR THE TREATMENT OF ACUTE OTITIS MEDIA (AOM), Daniel Burch, George -Aloonsamn@y. The A 011 Collaborative Stu@y Group,- SnÃ¼th-Kline Beecham Phariiaceuticals, Collegeville, PA, USA; Birmingham; UK. 21st International Congress of Chemotherapy. 7/4/1999

Clinical Profile of a New Formulation of Amoxicillin/Clavulanate (A/C) for the Treatment of Acne Otitis Media, Burch, D, MD; McCracken, G, MD; Moonsammy, G, MD; Acne Otitis Media Collaborative Study Group. Southwestern Medical Center, Dallas, Texas; SmithKline Beecham, Collegeville, Pennsylvania; San Francisco, CA; USA. *Infectious Diseases Society of America 35th Annual Meeting*. 9/13/1997

Date Updated: 11-Aug-2005