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<b>Study No:</b> 552	
<b>Title:</b> A two-part crossover study to assess the pharmacokinetics of amoxicillin after administration with clavulanate of pharmacokinetically enhanced formulations of amoxicillin in healthy volunteers.	
<b>Rationale:</b> In this study, the pharmacokinetic and pharmacodynamic profile of amoxicillin and clavulanate in five novel pharmacokinetically enhanced (PE) formulations were compared in order to select a formulation for further development. The aim of this new formulation was to provide more effective therapy against drug-resistant pathogens by increasing the plasma concentration of amoxicillin and clavulanate over a longer period of time to ensure susceptibility for <i>S. pneumoniae</i> close to 100%.	
<b>Phase:</b> I	
<b>Study Period:</b> 7 June 1999 to 7 July 1999.	
<b>Study Design:</b> Open-label, randomized, two-part crossover design. Randomization was stratified by gender.	
<b>Centres:</b> Single centre (Germany).	
<b>Indication:</b> None.	
<b>Treatment:</b> Each subject participated in two dosing sessions, separated by at least three days. Each subject received a single dose of the reference formulation and was randomly assigned to receive a single dose of one novel formulation: Formulation A: PE amoxicillin trihydrate 875mg, formulated to release over 4 hours (approximately 4% xanthan gum), co-administered with an amoxicillin/clavulanate 875/125mg tablet. Formulation B: PE amoxicillin trihydrate 875mg, formulated to release over 1 hour (approximately 0.5% xanthan gum), co-administered with an amoxicillin/clavulanate 875/125mg tablet. Formulation C: PE crystalline sodium amoxicillin 875mg, formulated to release over 4 hours (approximately 4% xanthan gum), co-administered with an amoxicillin/clavulanate 875/125mg tablet. Formulation D: PE crystalline sodium amoxicillin 875mg, formulated to release over 1 hour (approximately 2% xanthan gum, 156mg Citric acid), co-administered with an amoxicillin/clavulanate 875/125mg tablet. Formulation E: PE crystalline sodium amoxicillin 500mg, formulated to release over 4 hours (approximately 4% xanthan gum), co-administered with an amoxicillin/clavulanate 500/125mg tablet and a trihydrate amoxicillin 500mg tablet. Formulation F, Reference: One tablet of trihydrate amoxicillin 875mg and an amoxicillin/clavulanate 875/125mg tablet.	
<b>Objectives:</b> To assess amoxicillin pharmacokinetics of PE formulations of amoxicillin when co-administered orally with an amoxicillin/clavulanate tablet, in healthy male and female volunteers; to determine the combination which best meets the acceptance criteria for use in phase III clinical trials. The target PK values proposed included a mean time above the minimum inhibitory concentration (T>MIC) of amoxicillin at MIC of 4µg/mL to be at least 40% of the 12-hour dosing interval (i.e. to be at least 4.8 hours) and a mean maximum plasma concentration (C <sub>max</sub> ) to be equal to or greater than 16µg/mL (4 times MIC of 4µg/mL).	
<b>Statistical Methods:</b> Subjects were included in the pharmacokinetic analysis if they had evaluable data from both the novel and reference formulations. All subjects who received at least one dose of study medication were included in the evaluation of safety. Log <sub>e</sub> -transformed C <sub>max</sub> and untransformed T>MIC for each of the novel formulations were analysed using analysis of covariance (ANCOVA) fitting a single term for formulation and fitting the data from the reference formulation as a covariate. The 95% confidence intervals (CIs) for the means of each formulation were constructed using the residual variance from the model. For C <sub>max</sub> , the CI estimates on the log scale were then back-transformed to obtain the 95% CIs of the geometric mean.	
<b>Study Population:</b> Healthy male or female subjects, aged between 18-60 years, inclusive, who passed a comprehensive medical interview and were not allergic to penicillin antibiotics. Key exclusion criteria included use of any prescription or non-prescription medication, pregnancy, and positive hepatitis tests. Adequate contraceptive measures were required for females of child-bearing potential.	
<b>Number of Subjects:</b>	<b>All Subjects</b>
Planned, N	40
Dosed, N	40
Completed, n (%)	40 (100)
Total Number Subjects Withdrawn, n (%)	0
Withdrawn due to Adverse Events, n (%)	0

Withdrawn due to Lack of Efficacy, n (%)					Not applicable	
Withdrawn for Other Reasons, n (%)					0	
<b>Demographics</b>	<b>Formulation</b>					
	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>
N	8	8	8	8	8	40
Females: Males	4:4	4:4	4:4	4:4	4:4	20:20
Mean Age in Years (SD)	32 (10.9)	31 (7.0)	33 (5.1)	40 (9.2)	31 (10.3)	33 (9.0)
Mean Weight in Kg (SD)	76.1 (12.0)	69.9 (11.3)	67.4 (11.1)	70.2 (9.3)	68.9 (10.2)	70.5 (10.7)
Caucasian, n (%)	8 (100)	7 (87.5)	8 (100)	8 (100)	8 (100)	39 (97.5)
<b>Pharmacokinetic (PK) Results:</b>						
<b>Parameter, arithmetic mean (SD)</b>	<b>Formulation</b>					
	<b>A (N=8)</b>	<b>B (N=8)</b>	<b>C (N=8)</b>	<b>D (N=8)</b>	<b>E (N=8)</b>	<b>F (N=40)</b>
T>MIC 4 $\mu$ g/mL (h)	4.5 (1.8)	4.4 (0.7)	4.4 (0.9)	5.7 (2.5)	4.8 (0.9)	4.3 (0.8)
C <sub>max</sub> ( $\mu$ g/mL)	12.8 (4.96)	23.8 (10.6)	18.6 (4.72)	13.0 (2.34)	17.3 (4.62)	20.2 (6.09)
T <sub>max</sub> (h), median (range)	1.53 (0.50-4.00)	1.51 (1.00-3.02)	1.50 (1.00-2.02)	1.25 (1.00-6.02)	1.75 (1.00-3.00)	1.50 (0.98-3.00)
AUC <sub>(0-inf)</sub> ( $\mu$ g.h/mL)	48.2 (24.0)	69.1 (24.3)	57.6 (15.3)	57.8 (25.0)	57.3 (9.0)	56.5 (16.1)
T <sub>1/2</sub> (h)	1.42 (0.26)	1.23 (0.13)	1.29 (0.14)	1.93 (0.87)	1.44 (0.26)	1.31 (0.20)
AUC <sub>(0-inf)</sub> = Area under the plasma concentration-time curve from time zero to infinity; T <sub>1/2</sub> = Elimination half life; T <sub>max</sub> = Time to maximum plasma concentration.						
<b>Parameter</b>	<b>Formulation</b>		<b>Point Estimate</b>		<b>95% CI</b>	
C <sub>max</sub> ( $\mu$ g/mL)	A		12.66		10.52, 15.24	
	B		22.55		18.76, 27.10	
	C		16.25		13.46, 19.63	
	D		13.82		11.47, 16.65	
	E		15.88		13.19, 19.10	
T>MIC (h)	A		4.62		3.73, 5.50	
	B		4.57		3.68, 5.45	
	C		4.65		3.76, 5.54	
	D		5.55		4.66, 6.43	
	E		4.41		3.51, 5.30	
Point estimate represents the adjusted geometric mean for C <sub>max</sub> and adjusted arithmetic mean for T>MIC.						
<b>Safety Results: Safety Population -</b> Adverse events (AEs) were collected pre-dose, 12 hours after each study drug administration and at follow-up (7-14 days after the last dose).						
<b>Adverse Events:</b>	<b>Formulation</b>					
	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>
N	8	8	8	8	8	40
No. subjects with AEs, n (%)	3 (37.5)	2 (25.0)	4 (50.0)	2 (25.0)	4 (50.0)	13 (32.5)
Most Frequent AEs						
Headache	2 (25.0)	1 (12.5)	4 (50.0)	1 (12.5)	2 (25.0)	8 (20.0)
Diarrhoea	1 (12.5)	0	2 (25.0)	0	1 (12.5)	6 (15.0)
<b>Serious Adverse Events (SAEs), n (%) [n considered by the investigator to be related to study medication]</b>						
N	8	8	8	8	8	40
No. subjects with SAEs n (%) [related] -includes fatal and non-fatal events	0	0	0	0	0	0
<b>Publications:</b> No Publication						

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