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.

<table>
<thead>
<tr>
<th>Study No.: BRL-25000/668</th>
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</table>
| **Title:** An uncontrolled, phase I study to determine *ex vivo* the serum bactericidal activity against *Streptococcus pneumoniae* with decreased susceptibility to amoxicillin in the presence of factors of non-specific immunity with and without specific antibodies, the urine bactericidal activity against *Escherichia coli* with decreased susceptibility to amoxicillin/clavulanic acid (AMX/CA), and the selective faecal decontamination over a 72 h period after the administration of a single oral dose of 2000/125mg AMX/CA (Augmentin XR) to healthy volunteers.

| **Rationale:** A new formulation of AMX/CA (2000/125 mg), to be taken twice daily, has been designed with an enhanced pharmacokinetic profile. The pharmacokinetically enhanced AMX/CA formulation achieves amoxicillin serum concentrations that exceed the MIC against *S. pneumoniae* with amoxicillin MICs of 4 mg/l for 49% of the dosing interval and the MIC against *S. pneumoniae* with amoxicillin MICs of 8 mg/l for 35% of the dosing interval. Data from humanized animal models and clinical trials show therapeutic efficacy against *S. pneumoniae* strains with MIC of 4 and 8 µg/ml, supporting that it is needed to cover 25-40% of the dosing interval to obtain therapeutic efficacy with penicillins. The effect with non-specific immunity has been demonstrated against pencillin-resistant *S. pneumoniae* strains *in vitro* and *ex vivo* in a Phase I study with amoxicillin. With regard to specific immunity, several animal models have demonstrated the synergic effect, with respect to the mortality end point, of passively administered specific antibodies and amoxicillin. Immunization of animals resulted in antibiotic efficacy with pharmacodynamic parameters far below the values considered necessary for efficacy. On the other hand, there are no published data neither on pharmacokinetic urine profile nor on urine bactericidal activity of Augmentin XR. The increase of amoxicillin urinary concentration could be enough to provide coverage against *Escherichia coli* resistant strains to the conventional formulations of amoxicillin/clavulanic acid. Finally, the selective gut decontamination of *E. coli* can be important to avoid selection of resistance for the normal flora.

| **Phase:** I |
| **Study Period:** 20 Oct 2003 to 16 Feb 2004. |
| **Study Design:** A Phase I, open-label, noncomparative clinical trial in healthy volunteers. Volunteers received one single oral dose of AMX/CA 2000/125 mg. Three days after the antibiotic dosing, the volunteers received one deep subcutaneous administration of an *S. pneumoniae* polysaccharide vaccine. Sixty days after vaccination, the volunteers returned to the Clinical Pharmacology Unit and received a second oral single antibiotic dose. |
| **Centres:** 1 centre in Spain |
| **Indication:** N.A |
| **Treatment:** Subjects received a single oral dose of amoxicillin/clavulanic acid 2000/125 mg on the mornings of Day 1 and Day 60. Subjects also received one deep subcutaneous administration of a |
**Streptococcus pneumoniae** polysaccharide vaccine (Aventis Pasteur S.A., Marcy l’Etoile, France) three days after the first dose of antibiotics.

### Objectives:

**Primary objective:** To evaluate, after a single Augmentin XR oral dose to healthy volunteers, the following pharmacodynamic parameters:

- Serum bactericidal activity against 4 strains of *S. pneumoniae* with AMX minimal inhibitory concentrations (MICs) of 2, 4, 8 and 16 mg/L, measured as bacterial killing rates in the presence and absence of polymorphonuclear neutrophils (PMN) and complement with or without specific antibodies.
- Urine bactericidal activity against 4 strains of *E. coli* with amox/clav MICs of 8, 16, 32 and 64 mg/L measured as bacterial killing rates with urine samples collected at different intervals after dosing.
- Selective gut decontamination measured as percentage of reduction of counts of *E. coli* and global anaerobic flora in fecal samples collected after dosing with respect to pre-dosing samples.

**Secondary objective:**

- To determine the pharmacokinetic urine profile of amoxicillin/clavulanic acid 2000/125 mg after administration of a single dose.
- To determine serum pharmacodynamic parameters (ΔT>MIC) against several strains.

### Primary Outcome/Efficacy Variable:

a) Bacterial mortality rate in serum (defined as difference between AUKC<sub>k</sub> –bacterial growth curve- and AUKC –area under the killing curve- and/or differences in log<sub>10</sub> CFU/mL between initial inocula and final colony counts) in presence and absence of PMN and/or specific antibodies; b) Bacterial mortality rate in urine (defined as difference between AUKC<sub>k</sub> –bacterial growth curve- and AUKC –area under the killing curve- and/or differences in log<sub>10</sub> CFU/mL between initial inocula and final colony counts) in the urine samples collected at different intervals after dosing; c) Percentage of reduction of *E. coli* and gram negative anaerobic flora counts in faecal samples collected after dosing with respect to the basal sample.

### Secondary Outcome/Efficacy Variable(s):

a) AMX/CA serum concentration over 12 h after administration of a single dose of AMX/CA sustained release; b) AMX/CA urine concentration over 72 h after administration of a single dose of AMX/CA sustained release; c) Serum pharmacodynamic parameters (ΔT>MIC) against study strains.

### Statistical Methods:

- Serum bactericidal activity against *S. pneumoniae* was studied using the area under the killing curve (AUKC; log cfu x h/mL) as a measure of global killing over 3 h of incubation. Bacterial growth curve (AUKC<sub>k</sub>) was the control. Difference between AUKC<sub>k</sub> and AUKC obtained with inactivated serum, with inactivated serum plus PMN, with active serum and with active serum plus PMN were determined. Owing to multiple comparisons, a *P* value <0.005 was considered significant; b) Differences in log<sub>10</sub> CFU/mL between initial inocula and final colony counts were determined. Owing to multiple comparisons, a *P* value <0.005 was considered significant.

### Study Population:

| Planned, N | 12 |
| Entered, N | 12 |
| Completed, n (%) | 12 (100%) |
| Total Number Subjects Withdrawn, N (%) | 0 (0%) |
| Withdrawn due to Adverse Events n (%) | 0 (0%) |
| Withdrawn due to Lack of Efficacy n (%) | 0 (0%) |
| Withdrawn for other reasons n (%) | 0 (0%) |

**Demographics**

| N (ITT) | 12 |
| Females: Males | 0:12 |
| Mean Age, years (SD) | 24.83 (5.8) |
| Caucasian, (%) | 11 (91.7%) |

**Primary Efficacy Results:**

<table>
<thead>
<tr>
<th>Population</th>
<th>AMX/CA</th>
</tr>
</thead>
</table>
| ITT (N=12) | - Significant differences in bactericidal activity against *S. pneumonia* were found between active serum and inactivated serum for those therapeutic indexes ranging from 1.13 to 3.04. Significant differences in bactericidal activity was found between active serum + PMN versus inactivated serum for therapeutic indexes ranging from 0.56 to 3.04; however, when the therapeutic index was 6.08, significance was nearly reached (*P*=0.007).
- Significant differences in mean antibacterial activity vs *E. coli* (log10 initial inoculum and log10 CFU/mL after 4 h incubation) in urine were found up to 12 h after dosing for strains with MICs 8/4, 16/8 and up to 8 h for strain with MICs 32/16 and 64/32 µg/mL (all *P* < 0.005).
- At 72h, a small increase of *E. coli* counts (increase of 1.59 log10 UFC/ g) and gram positive bacteria counts, mainly *Enterococcus*, (increase of 1.17 log10 UFC/ g) was observed with respect to the basal sample. No variations were observed regarding yeasts and gram negative anaerobic bacteria (*B. fragilis*). |

| On-Treatment (N=12) | NA |

**Secondary Outcome Variable(s):**

a) AMX PK/PD parameters: $T_{\text{max}}$ (h) 1.96 ± 0.99; $C_{\text{max}}$ (mg/L) 13.45 ±1.81; $AUC_{\text{last}}$ (mg/L x h) 53.36 ±11.35;

b) AMX concentrations (µg/mL) in urine after a single dose [mean (SD)]: 436.57 (402.03) at 0-2 h;
814.72 (373.24) at 2-4 h; 490.47 (247.37) at 4-8 h; 130.72 (118.26) at 8-12 h; 21.51 (16.12) at 12-16 h; 5.87 (3.53) at 16-24 h; 0.36 (0.16) at 24-36 h; 0.14 (0.08) at 36-48 h; 0.06 (0.01) at 48-60 h; e) \( t > \text{MIC}_{\text{serotype } 14} \) (MIC 16 mg/L): 0% of dosing interval; \( \text{MIC}_{\text{serotype } 9V} \) (MIC 8 mg/L): 24.05 ± 6.75% of dosing interval; \( \text{MIC}_{\text{serotype } 6B} \) (MIC 4 mg/L): 43.26 ± 9.15% of dosing interval; \( \text{MIC}_{\text{serotype } 23F} \) (MIC 2 mg/L): 56.42 ± 9.71% of dosing interval

### Safety Results:

<table>
<thead>
<tr>
<th>Adverse events related to study medication</th>
<th>AMX/CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE(s), n (%)</td>
<td>N=12</td>
</tr>
<tr>
<td><strong>Most Frequent Adverse Events – On-Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Increased CPK</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Increased GPT</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Microhematuria</td>
<td>1 (8)</td>
</tr>
<tr>
<td><strong>Serious Adverse Event (SAE):</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

### Conclusion:

An increase in the global killing of \( S. pneumoniae \) by amoxicillin/clavulanic acid occurs over 3h by opsonophagocytosis mediated by complement activated by specific antibodies, or to a lesser extent by killing due to complement activated by specific antibodies suggesting that collaboration of the immune system and amoxicillin/clavulanic acid may overcome in vivo amoxicillin non-susceptibility.

Once daily dosing of amoxicillin/clavulanic acid may not be effective in the treatment of acute cystitis caused by \( E. coli \). However, twice daily dosing would extend coverage to intermediately resistant strains in the urine.

### Publications:


Date Updated: 31 October 2008