Oral pharmacokinetically enhanced co-amoxiclav 2000/125 mg, twice daily, compared with co-amoxiclav 875/125 mg, three times daily, in the treatment of community-acquired pneumonia in European adults

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Objectives: Pharmacokinetically enhanced co-amoxiclav 2000/125 mg was designed to achieve high serum concentrations of amoxicillin over the 12 h dosing interval to eradicate Streptococcus pneumoniae with amoxicillin MICs of at least 4 mg/L.

Methods: This randomized, double-blind, double-dummy, multicentre study compared the efficacy and safety of oral co-amoxiclav 2000/125 mg twice daily versus co-amoxiclav 875/125 mg three times daily, for 7 or 10 days, in the treatment of community-acquired pneumonia (CAP).

Results: The per-protocol (PP) population at follow-up (Days 18–39) comprised 114 patients receiving co-amoxiclav 2000/125 mg and 116 receiving co-amoxiclav 875/125 mg. Clinical success at follow-up (primary efficacy endpoint) in the clinical PP population was 94.7% (108/114) for co-amoxiclav 2000/125 mg versus 88.8% (103/116) for co-amoxiclav 875/125 mg [treatment difference (TD) = 5.9%, 95% CI: 1.1, 13.0]. Bacteriological success in the bacteriology PP population at follow-up was 85.0% (17/20) for co-amoxiclav 2000/125 mg versus 77.3% (17/22) for co-amoxiclav 875/125 mg (TD = 7.7%, 95% CI: 15.8, 31.2). Penicillin-resistant S. pneumoniae (PRSP) were isolated in three patients (including two with bacteraemia) in the co-amoxiclav 2000/125 mg group (amoxicillin MICs 8 mg/L, penicillin MICs 4 mg/L) and one in the comparator group; all were clinical and bacteriological successes. Co-amoxiclav 2000/125 mg and co-amoxiclav 875/125 mg were associated with adverse events leading to withdrawal in 6.3% and 6.2% of patients, respectively.

Conclusions: Co-amoxiclav 2000/125 mg twice daily was at least as effective clinically as co-amoxiclav 875/125 mg three times daily in the treatment of CAP. Although few patients in this study had PRSP infection, 3/3 were successfully treated with co-amoxiclav 2000/125 mg.

Keywords: Streptococcus pneumoniae, CAP, antimicrobials

Introduction

Community-acquired pneumonia (CAP) is a common illness worldwide and is associated with significant morbidity and mortality. The incidence of CAP has been estimated to be one-to-three cases per 1000 adult population in the UK1 and 12 attacks per 1000 adults annually in the USA.2 The mean mortality rate of patients with CAP is 14% among hospitalized patients, but may be lower than 1% for non-hospitalized patients.3

In 40%–60% of diagnoses of CAP, the cause of pneumonia cannot be determined,3 however, the most frequently isolated causative organism is Streptococcus pneumoniae.4

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MICs ≥ 1 mg/L in 1998–2000 was 27.5% in Spain and 35.2% in Italy. Up to 10% of all S. pneumoniae strains may be resistant to multiple agents. The correlation between penicillin and macrolide resistance observed in Spain is of concern, as the increasing use of long-acting macrolides may accelerate the development of antimicrobial resistance in S. pneumoniae.

Co-amoxiclav (amoxicillin + clavulanate, Augmentin) is an oral agent licensed for use in patients with CAP that is suspected to be caused by pneumococci and/or β-lactamase-producing pathogens. S. pneumoniae susceptibility to conventional formulations of co-amoxiclav was 95.5% worldwide in 1998–2000 and 90.4% in Spain in 1998–1999.

Although conventional formulations of co-amoxiclav, such as co-amoxiclav 875/125 mg three times daily prescribed in Spain, Italy, Portugal, Austria and Switzerland, are still effective oral treatments for respiratory tract infections, the increasing prevalence of antimicrobial resistance in certain regions indicates an emerging need for new therapies and novel formulations of existing agents. Strains of S. pneumoniae with reduced susceptibility to penicillin can be overcome by higher doses of the more potent β-lactams without substantially increasing the risk of adverse reactions. Although the clavulanate component of co-amoxiclav does not contribute to the activity of the antimicrobial against S. pneumoniae, it does protect the amoxicillin component from degradation by β-lactamases produced by other pathogens that cause CAP, such as Haemophilus influenzae and Moraxella catarrhalis, both commonly isolated pathogens in CAP. As most therapy for CAP is empirical, the coverage of β-lactamase-producing organisms is valuable.

A new pharmakokinetically enhanced formulation of co-amoxiclav (2000/125 mg) provides a maximum amoxicillin plasma concentration of at least 16 mg/L. Each 1000/62.5 mg tablet contains a layer of immediate-release amoxicillin trihydrate plus clavulanate potassium, and a layer of sustained-release sodium amoxicillin. Two tablets are taken every 12 h. For S. pneumoniae strains with amoxicillin MICs of 4 mg/L, co-amoxiclav 2000/125 mg achieves serum concentrations exceeding the MIC for 49% (95% CI: 47%, 52%) of a 12 h dosing interval, whereas the standard 875/125 mg formulation exceeds an MIC of 4 mg/L for only 34% of the dosing interval. C. Kaye, GlaxoSmithKline, Welwyn, UK, personal communication. For S. pneumoniae strains with amoxicillin MICs of 8 mg/L, serum concentrations of co-amoxiclav 2000/125 mg exceed the MIC for ~35% of the dosing interval. Previous animal studies and studies in otitis media and sinusitis in humans have shown that a time above the MIC (T > MIC) of 35%–40% is necessary for bacteriological efficacy. The pharmacokinetic properties of clavulanate are not affected by the addition of an extended-release component, compared with standard co-amoxiclav formulations. Thus, the new formulation containing sustained-release amoxicillin is predicted to achieve improved coverage for PRSP, including amoxicillin-non-susceptible isolates, compared with existing immediate-release formulations, while maintaining activity against H. influenzae and M. catarrhalis, including β-lactamase-producing strains.

This study compared the efficacy and safety of the oral pharmacokinetically enhanced formulation of co-amoxiclav 2000/125 mg twice daily with that of oral co-amoxiclav 875/125 mg three times daily in the treatment of CAP in adults for 7 or 10 days.

Materials and methods

Study design

This randomized, double-blind, double-dummy, parallel-group, Phase III clinical trial was conducted in 20 centres in Spain and 12 centres in Italy during January 2000–January 2001. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki as amended in Somerset West, Republic of South Africa, in 1996. The protocol was approved by local ethics committees, and written, dated, informed consent was obtained from patients prior to study entry.

Patient selection

The study included adult patients (218 years old) with radiologically confirmed CAP. A chest X-ray performed within 48 h prior to enrolment or study entry, demonstrating new or progressive infiltrate(s) or consolidation consistent with pneumonia, was required. Patients were eligible for enrolment if they had a fever or history of fever for the current episode of CAP plus at least one of the following: new or increased cough; purulent sputum or a change in sputum characteristics; pulmonary rales and/or signs of consolidation; dyspnoea or tachypnoea; peripheral white blood cell (WBC) count of >10 000 cells/mm³, or >15% immature neutrophils regardless of total WBC count, or leucopenia with <4500 cells/mm³ of total WBC count; a partial oxygen pressure of <60 mmHg. To be included in the study, patients had to provide a sputum sample or an invasive respiratory sample. Women of child-bearing potential must have had a negative urine pregnancy test prior to enrolment and were required to take adequate contraceptive precautions throughout the study period. Both hospitalized and ambulatory patients were included in the study.

Patients with known or suspected hypersensitivity to penicillin or related antimicrobials were excluded from the study. Patients were also excluded if they had: pneumonia suspected by the physician to be caused by atypical pathogens; aspiration or post-obstructive pneumonia; hospital-acquired pneumonia; been hospitalized within 2 weeks prior to enrolment; a serious unstable underlying disease; cystic fibrosis, active tuberculosis, bronchiectasis or active pulmonary malignancies; active infectious mononucleosis; known or suspected renal or hepatic impairment. Immunosuppressed or HIV-positive patients (with a CD4 count of <200 cells/mm³), patients actively abusing alcohol or drugs, and pregnant or breastfeeding women were not eligible for enrolment. Patients requiring parenteral antimicrobial therapy and those who had received >24 h of treatment with any other antimicrobial for the current episode of CAP within 7 days prior to enrolment were also excluded from the trial.

Randomization and study medication

Eligible patients were randomized (1:1) to receive either oral co-amoxiclav 2000/125 mg (as two tablets) twice daily plus oral co-amoxiclav 875/125 mg (as one tablet) or oral co-amoxiclav 875/125 mg (as one tablet) three times daily plus oral co-amoxiclav (2000/125 mg)-placebo (as two tablets) twice daily. Therapy lasted for 7 or 10 days depending on the severity of the disease as assessed at the on-therapy visit by the investigator. To maintain investigator blinding, randomization and assignment to a treatment group was performed centrally via an interactive telephone-based system.

Assessment of compliance

All patients were provided with a 10 day supply of study medication. At the on-therapy visit, the investigator determined whether therapy was required for 7 or 10 days and, if only 7 days’ therapy was necessary, would remove 3 days’ worth of medication from the patient’s supply. The number of tablets taken over the first 72 h of therapy was determined.
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At the on-therapy visit, patients were considered compliant if they had taken 100% of allocated study medication for the first 72 h of therapy.

At the end-of-therapy visit, patients returned any unused medication and a count of unused tablets was performed by the investigator. Patients were considered compliant if they had taken 100% of the intended regimen for the first 72 h of treatment and between 80%–120% of the intended regimen overall.

Efficacy evaluation

Patients were required to attend the clinic on four occasions: at study entry (Day 0), on-therapy (Days 3–5), at end of therapy (Days 9–14) and at follow-up (Days 28–35).

The primary efficacy parameter was clinical response at follow-up. Secondary efficacy parameters were clinical response at end of therapy, bacteriological response at end of therapy and at follow-up, and radiological response at end of therapy and at follow-up.

A clinical response of success at either follow-up or end of therapy was defined as a clinical outcome of ‘success’ for that visit (sufficient improvement or resolution of the signs and symptoms of CAP recorded at study entry such that no additional antimicrobial therapy was indicated for CAP). A clinical response of failure at end of therapy was defined as an end-of-therapy clinical outcome of ‘failure’ or ‘unable to determine’. Clinical failure at follow-up was defined as a follow-up clinical outcome of ‘clinical recurrence’ or ‘unable to determine’, or an end-of-therapy clinical outcome of ‘failure’ or ‘unable to determine’.

The per-patient bacteriological response was successful at end of therapy or at follow-up if all initial pathogens were eradicated or presumed to have been eradicated (based on a successful clinical outcome in the absence of an evaluable sputum or respiratory sample) at the end-of-therapy or follow-up visits, respectively, and there was no superinfection or new infection.

Radiological success at end of therapy and at follow-up, respectively, was defined as a radiological outcome of ‘improved’ (improvement or resolution of radiological signs of CAP) and an outcome of ‘improved’ or ‘presumed improved’ (a derived outcome for patients with an outcome of ‘unable to determine’: clinical success at follow-up and improved radiological outcome at end of therapy).

The therapeutic response at end of therapy and at follow-up was successful if both the clinical and bacteriological responses at the respective time point were successes.

Bacteriology

Sputum or invasive respiratory samples were obtained at study entry and, where possible, at end of therapy, follow-up or time of failure or withdrawal. Sputum samples were considered evaluable for routine culture if they were purulent (using Gram stain: >25 WBCs per field and <10 Gram staining, culture, semi-quantification and identification of isolates were performed at the local laboratory. All pathogens were then sent to a central laboratory (Quest Diagnostics, Heston, UK) for confirmation of identification, susceptibility testing and storage.

MICs for aerobic pathogens were determined by broth microdilution according to NCCLS guidelines.18 Susceptibility of all pathogens to co-amoxiclav was also tested by disc diffusion.19 MIC values for co-amoxiclav were based on the amoxicillin component. Serological testing of blood samples taken at study entry and at follow-up for atypical pathogens (Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae, Chlamydia psittaci and Coxiella burnetii) was conducted by the central laboratory and MRL Diagnostics (Cypress, CA, USA). A determination of sero-positive results was based on an increase from baseline titre value in subsequent blood samples. A Legionella urine antigen test (Binax, Portland, ME, USA) was carried out at study entry and patients with positive results were withdrawn from the study.

The NCCLS breakpoints19 used for co-amoxiclav and S. pneumoniae were: susceptible, ≤2 mg/L; intermediate, 4 mg/L; resistant, ≥8 mg/L; those used for penicillin were: susceptible, ≤0.06 mg/L; intermediate, 0.12–1 mg/L; resistant, ≥2 mg/L.

Safety assessments

Adverse experiences were recorded during therapy and for 30 days post-therapy, and their severity and relationship to study medication were assessed.

Statistical analysis

Four patient populations were defined for the efficacy analyses: the intent-to-treat (ITT) population (all randomized patients who took at least one dose of study medication), the clinical per-protocol (PP) population (excluding patients who violated any aspect of the protocol to an extent that may have affected the evaluation of treatment efficacy), the bacteriology ITT population (all randomized patients who took at least one dose of study medication and had at least one typical pre-therapy pathogen identified at study entry) and the bacteriology PP population (excluding patients who violated any aspect of the protocol to an extent that may have affected the evaluation of treatment efficacy). In this study, to show non-inferiority, the PP population was considered as the primary population for efficacy. For the safety evaluations, the ITT population was considered the primary population.

The study was designed to enrol 320 patients in order to have –120 clinically evaluable patients in each treatment arm, assuming an underlying equivalent clinical response of 85% at follow-up and that up to 25% of patients would not be eligible for the clinical PP population. Before breaking the study blind, the protocol-specific windows for three of the visits were extended for the purpose of analysis: study entry was extended from Day 0 to Day –2 to 1, end of therapy from Days 9–14 to Days 8–17 and follow-up from Days 28–35 to Days 18–39.

Two-sided 95% confidence intervals (CIs) were used to estimate the difference in the proportion of successes between the two treatment groups. A conclusion of non-inferiority of co-amoxiclav 2000/125 mg could be drawn if the lower limit of the CI (co-amoxiclav 2000/125 mg minus co-amoxiclav 875/125 mg) was no less than –15%.20

Fisher’s exact test was used to compare the proportions of patients in the two treatment groups who reported adverse experiences or who withdrew from the study, and to compare treatment compliance between the two groups. Two-sided 95% CIs were calculated for the differences in proportions between the treatment groups.

Results

Patient disposition and baseline characteristics

A total of 320 patients were randomized, 158 to receive co-amoxiclav 2000/125 mg twice daily and 162 to receive co-amoxiclav 875/125 mg three times daily (Figure 1). Overall, all but one patient in the co-amoxiclav 875/125 mg group received at least one dose of study medication. The co-amoxiclav 2000/125 mg group included 122 patients from Spain plus 36 from Italy, and the comparator group included 125 patients from Spain plus 36 from Italy.

The clinical PP population at end of therapy and follow-up, respectively, excluded 20.3% and 27.8% of patients treated with co-amoxiclav 2000/125 mg, and 20.5% and 28.0% of those treated with co-amoxiclav 875/125 mg (Figure 1).
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There were no major differences in demographic or clinical characteristics between the groups in the ITT and clinical PP follow-up populations or between the two populations (Table 1). However, in the co-amoxiclav 2000/125 mg group, a slightly higher proportion of patients had a smoking history of >30 pack-years, and there were slightly more patients with a change in sputum characteristics compared with the co-amoxiclav 875/125 mg group (Table 1).

Compliance with study medication in the ITT population was similar between the two treatment groups: 142/158 (89.9%) in the co-amoxiclav 2000/125 mg group versus 139/161 (86.3%) in the co-amoxiclav 875/125 mg group (treatment difference = 3.5%, 95% CI: −3.6, 10.6; \( P = 0.39 \)). The mean duration of exposure in the ITT population was similar for the two treatment groups: 8.4 days for co-amoxiclav 2000/125 mg and 8.2 days for co-amoxiclav 875/125 mg.

In the ITT population, 65/158 (41.1%) patients in the co-amoxiclav 2000/125 mg group and 65/161 (40.4%) in the co-amoxiclav 875/125 mg group had their treatment extended from 7 to 10 days at the on-therapy visit, based on the investigator’s assessment of disease severity. In the clinical PP population, treatment was extended for 45/114 (39.5%) patients in the co-amoxiclav 875/125 mg group and 49/116 (42.2%) patients in the co-amoxiclav 2000/125 mg group.

Bacteriology
Sixty patients (30 in each treatment arm) had at least one pathogen identified by culture at study entry and were therefore included in the

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Figure 1. Flow chart of patients’ progress through the study. AMX/CA, co-amoxiclav.
bacteriology ITT population. This pathogen recovery rate was affected by the number of sputum samples that did not meet the Gram-stain criteria (56.8%). At end of therapy, seven patients in the co-amoxiclav 2000/125 mg group and four in the co-amoxiclav 875/125 mg group were excluded from the bacteriology PP population, and 10 and eight patients, respectively, were excluded from this population at follow-up. Major reasons for exclusion were non-compliance with medication, non-compliance with clinic visits and concomitant medication. Concomitant medications leading to exclusion could include the use of any prohibited medication detailed in the exclusion criteria or use of an antimicrobial prescribed for an indication other than CAP.

In the bacteriology ITT population, seven patients (4.4%) in the co-amoxiclav 2000/125 mg group and nine patients (5.6%) in the co-amoxiclav 875/125 mg group were bacteraemic, of whom five and six patients, respectively, were included in the clinical PP population at follow-up.

*S. pneumoniae* was the most frequently isolated pathogen (Table 2). *S. pneumoniae* was also the pathogen most frequently isolated from blood samples, being identified in five bacteraemic patients in the co-amoxiclav 2000/125 mg group and five in the co-amoxiclav 875/125 mg group in the bacteriology PP follow-up population. Two bacteraemic patients in the co-amoxiclav 2000/125 mg group (bacteriology PP follow-up population) were also seropositive for *C. pneumoniae*. In the co-amoxiclav 875/125 mg group, two patients with *S. pneumoniae* were also seropositive for atypical pathogens, one for *M. pneumoniae*, and the other for *C. burnetii*. The remaining bacteraemic patient in the bacteriology PP follow-up population had *H. influenzae* isolated at screening and was also seropositive for *C. burnetii*.

In the bacteriology PP follow-up population, two *S. pneumoniae* isolated at study entry from patients receiving co-amoxiclav 2000/125 mg had elevated co-amoxiclav MICs (8 mg/L), both of which were also resistant to penicillin (MICs 4 mg/L) and were isolated from blood samples. A third patient had two PRSP strains isolated from sputum, with penicillin and co-amoxiclav MICs of 2 mg/L. For the purpose of analysing bacterial outcomes, these strains were counted as a single isolate. There were no *S. pneumoniae* strains with co-amoxiclav MICs ≥ 4 mg/L isolated from patients in the co-amoxiclav 875/125 mg group in the bacteriology PP follow-up population, but one patient had PRSP strains (penicillin MICs 2 mg/L, co-amoxiclav MICs 1 mg/L) isolated from both blood and sputum.

### Clinical efficacy

The clinical success rate for co-amoxiclav 2000/125 mg in the clinical PP population at follow-up (Days 28–32, primary efficacy parameter) was high at 94.7% (108/114), compared with 88.8%...
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Table 2. Pathogens associated with CAP isolated in >1 patient at study entry in the bacteriology ITT and PP follow-up populations

<table>
<thead>
<tr>
<th>Pre-therapy pathogen</th>
<th>bacteriology ITT population</th>
<th>bacteriology PP population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>co-amoxiclav 2000/125 mg (n = 30)</td>
<td>co-amoxiclav 875/125 mg (n = 30)</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>18 (60.0)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>7 (23.3)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>MRSA</td>
<td>1 (3.3)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>MSSA</td>
<td>3 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td><em>Haemophilus parainfluenza</em></td>
<td>1 (3.3)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>2 (6.7)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td><em>C. pneumoniae</em></td>
<td>3 (10.0)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td><em>C. burnetii</em></td>
<td>3 (10.0)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td><em>M. pneumoniae</em></td>
<td>3 (10.0)</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

*a*Patients may have had >1 pathogen.
MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 3. Clinical, radiological and bacteriological per-patient success rates for co-amoxiclav 2000/125 mg and 875/125 mg at end of therapy for the ITT and PP populations, and bacteriological per-pathogen success rates at end of therapy and follow-up for the PP population

<table>
<thead>
<tr>
<th>Success n/N (%)</th>
<th>co-amoxiclav 2000/125 mg</th>
<th>co-amoxiclav 875/125 mg</th>
<th>Treatment difference (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP at end of therapy</td>
<td>121/126 (96.0)</td>
<td>118/128 (92.2)</td>
<td>3.8</td>
<td>−1.9, 9.6</td>
</tr>
<tr>
<td>ITT at end of therapy</td>
<td>139/138 (88.0)</td>
<td>133/161 (82.6)</td>
<td>5.4</td>
<td>−2.4, 13.1</td>
</tr>
<tr>
<td>Bacteriological per-patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP at end of therapy</td>
<td>21/23 (91.3)</td>
<td>21/26 (80.8)</td>
<td>10.5</td>
<td>−8.5, 29.6</td>
</tr>
<tr>
<td>ITT at end of therapy</td>
<td>24/30 (80.0)</td>
<td>22/30 (73.3)</td>
<td>6.7</td>
<td>−14.7, 28.0</td>
</tr>
<tr>
<td>Bacteriological per-pathogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP at follow-up</td>
<td>20/24 (83.3)</td>
<td>18/23 (78.3)</td>
<td>5.0</td>
<td>NA</td>
</tr>
<tr>
<td>PP at end of therapy</td>
<td>25/27 (92.6)</td>
<td>22/27 (81.5)</td>
<td>11.1</td>
<td>NA</td>
</tr>
<tr>
<td>Radiological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical PP at end of therapy</td>
<td>111/126 (88.1)</td>
<td>111/128 (86.7)</td>
<td>1.4</td>
<td>−6.8, 9.5</td>
</tr>
<tr>
<td>Clinical ITT at end of therapy</td>
<td>125/158 (79.1)</td>
<td>127/161 (78.9)</td>
<td>0.2</td>
<td>−8.7, 9.2</td>
</tr>
</tbody>
</table>

n, number of clinical successes; N, number of isolates with the specified MIC.
NA, data not available. The 95% CI was not calculated due to lack of independence of per-pathogen outcomes when a patient had multiple pathogens.

For the pathogen most frequently isolated at study entry (*S. pneumoniae*), clinical success in the bacteriology PP follow-up population was high in both groups: 86.7% (13/15) for co-amoxiclav 2000/125 mg versus 92.3% (12/13) for co-amoxiclav 875/125 mg. The three patients with *S. pneumoniae* infections who were considered clinical failures all required additional antimicrobial therapy for pneumonia following treatment with the study medication. Of these three patients, two received intravenous ceftriaxone (one for 8 days plus 9 days of oral clarithromycin and one for 21 days plus 7 days of intravenous vancomycin hydrochloride) and the third received oral clarithromycin for an acute exacerbation of chronic bronchitis 6 days
after ending CAP therapy. Two of these patients also had co-infections: one with *H. influenzae* and one with *Serratia marcescens*. The third patient showed evidence of recent or concurrent infection with *C. pneumoniae*, based on paired serological testing results. Table 4 shows the clinical success rates by co-amoxiclav and penicillin MICs for *S. pneumoniae*. All of the patients in the bacteriology PP population infected by *S. pneumoniae* resistant to penicillin (MICs 2-4 mg/L) were clinical successes at follow-up in both treatment groups. Patients who had *S. pneumoniae* with elevated co-amoxiclav MICs isolated at screening (one with an MIC of 2 mg/L and two with MICs of 8 mg/L, all in the co-amoxiclav 2000/125 mg group) were all clinical successes at test of cure.

In the clinical PP follow-up population, the presence of an atypical pathogen did not appear to affect the efficacy of either therapy. For patients treated with co-amoxiclav 2000/125 mg, clinical success rates at follow-up were 93.3% (14/15) in patients with only typical pathogens, 75.0% (3/4) in patients with both a typical pathogen and serological evidence of an atypical pathogen, and 100% (30/30) in patients with serological evidence of an atypical pathogen, but with no typical pathogens isolated. For patients treated with co-amoxiclav 875/125 mg, the clinical success rates for these three groups were 73.3% (11/15), 85.7% (6/7) and 86.7% (26/30), respectively.

**Bacteriological efficacy**

In the bacteriology PP population at follow-up, 85.0% (17/20) of patients receiving co-amoxiclav 2000/125 mg were bacteriological successes, compared with 77.3% (17/22) of those receiving co-amoxiclav 875/125 mg (treatment difference = 7.7%, 95% CI: 15.8, 31.2) (Figure 2). In the bacteriology ITT population, the per-patient bacteriological success rates were 70.0% (21/30) and 66.7% (20/30) for co-amoxiclav 2000/125 mg and co-amoxiclav 875/125 mg, respectively (treatment difference = 3.3%, 95% CI: 20.2, 26.9) (Figure 2). Other per-patient bacteriological outcomes are shown in Table 3; there were no differences between the treatment groups.

Per-pathogen bacteriological success in the bacteriology PP population at follow-up was 83.3% for co-amoxiclav 2000/125 mg and 78.3% for co-amoxiclav 875/125 mg (Table 3). In patients receiving
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coa-amoxiclav 2000/125 mg, one of 24 pathogens (4.2%) was confirmed eradicated, and 19/24 (79.2%) were presumed eradicated. In patients receiving co-amoxiclav 875/125 mg, there were no isolates confirmed eradicated; however, 18/23 (78.3%) were presumed eradicated. Of the 24 isolates identified in the co-amoxiclav 2000/125 mg treatment group, one isolate (4.2%) was confirmed as persistent, as were two of the 23 isolates (8.7%) in the co-amoxiclav 875/125 mg treatment group. Three in each treatment group (12.5% and 13.0%, respectively) were presumed to be persistent or recurrent. The per-pathogen bacteriological success rates at end of therapy are shown in Table 3.

Co-amoxiclav 2000/125 mg was bacteriologically successful at follow-up in 4/5 (80.0%) bacteraemic patients in the clinical PP population, including two with PRSP isolated at study entry. The patient who was not considered a bacteriological success was not a clinical success and withdrew from the study at the on-therapy visit. A blood culture taken at that visit, however, yielded no growth. The corresponding bacteriological success rate for co-amoxiclav 875/125 mg in bacteraemic patients was 6/6 (100%), including one patient with PRSP.

For *S. pneumoniae*, 13/15 (86.7%) isolates in the bacteriology PP follow-up population were eradicated or presumed eradicated in the co-amoxiclav 2000/125 mg group versus 12/13 (92.3%) in the co-amoxiclav 875/125 mg group. The bacteriology results for *S. pneumoniae* by co-amoxiclav and penicillin MICs were the same as the clinical results in the bacteriology PP population at follow-up (Table 4), and thus all of the isolates resistant to current formulations of these agents were bacteriological successes.

Radiological efficacy

At follow-up, 94.7% (108/114) of co-amoxiclav 2000/125 mg-treated patients and 87.9% (102/116) of co-amoxiclav 875/125 mg-treated patients were radiological successes in the clinical PP population, and 82.3% (130/158) and 77.6% (125/161), respectively, were radiological successes in the ITT population (Figure 2). The radiological success rates at end of therapy were comparable between the two treatment groups and are shown in Table 3.

Therapeutic response

The therapeutic success rate (combined clinical and bacteriological response) for co-amoxiclav 2000/125 mg was higher than that for co-amoxiclav 875/125 mg in both bacteriology populations at end of therapy and at follow-up, although the difference was not statistically significant. At end of therapy, therapeutic success was reported in 91.3% (21/23) versus 76.9% (20/26) of patients, respectively, in the bacteriology PP population and in 76.7% (23/30) versus 70.0% (21/30), respectively, in the bacteriology ITT population. At follow-up, 85.0% (17/20) versus 77.3% (17/22) of patients, respectively, were therapeutic successes in the bacteriology PP population and 70.0% (21/30) versus 66.7% (20/30), respectively, were therapeutic successes in the bacteriology ITT population.

Safety results

During the interval on-therapy plus 30 days post-therapy, 40/158 (25.3%) patients in the co-amoxiclav 2000/125 mg group and 30/161 (18.6%) in the co-amoxiclav 875/125 mg group reported at least one adverse event with suspected or probable relationship to study medication (Table 5). Diarrhoea was the most frequently reported adverse event with suspected or probable relationship to the study medication, reported by 26/158 (16.5%) patients receiving co-amoxiclav 2000/125 mg and 21/161 (13.0%) receiving co-amoxiclav 875/125 mg (Table 5); all of these cases were of mild or moderate severity, and only three (1.9%) and four (2.5%) patients, respectively, required corrective treatment for this adverse event. No patients in either treatment group reported diarrhoea as a serious adverse event, and no cases of diarrhoea were caused by *Clostridium difficile*. Withdrawals due to adverse and other complicating events were low in both groups [6.3% (10/158) in the co-amoxiclav 2000/125 mg group and 6.2% (10/161) in the co-amoxiclav 875/125 mg group] (Table 6).

There were no deaths among study patients recorded on-therapy or within 30 days after therapy.

Discussion

This randomized, controlled trial demonstrated that the clinical efficacy of the new formulation of co-amoxiclav, 2000/125 mg twice daily, was at least as good as that of the 875/125 mg three-times-daily formulation in the 7–10 day treatment of CAP in adults. The high rate of clinical efficacy of co-amoxiclav 2000/125 mg shown in this study (94.7% in the clinical PP population at follow-up) is consistent with the 91.5% success rate observed in a previous study in CAP using a co-amoxiclav formulation prescribed in France (1000/125 mg three times daily) as the comparator.21

Overall, only 18.8% (60/319) of patients had at least one bacterial pathogen isolated at study entry. This low pathogen recovery rate reflected the high number of sputum samples (56.8%) that did not meet the Gram-stain criteria. As the majority of patients in this study had mild pneumonia, this percentage would be a reasonable expectation for evaluable samples.

Co-amoxiclav 2000/125 mg achieved therapeutic success in 85.0% of patients in the bacteriology PP population at follow-up, compared with 77.3% bacteriological success for co-amoxiclav 875/125 mg. Four of the eight therapeutic failures were associated with pathogens rarely associated with CAP (*S. marcescens*, *Burkholderia cepacia*, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*). However, due to the conservative protocol of the study, these patients were classed as failures based on the presence of a pathogen, regardless of relationship to the indication being treated.

Spain and Italy have both been reported in recent years to have a high prevalence of PRSP, and this prevalence varies among regions.5–7 Thus, by selecting centres in these two countries, this investigation aimed to capture several PRSP isolates for study. In the ITT population, 3/18 (16.7%) patients with *S. pneumoniae* who received co-amoxiclav 2000/125 mg and 2/16 (18.7%) who received co-amoxiclav 875/125 mg were found to have PRSP infections (penicillin MICs 2–4 mg/L). The four patients with PRSP isolates who were included in the bacteriology PP population were both clinical and bacteriological successes at follow-up. The PRSP isolates from two of the patients in the co-amoxiclav 2000/125 mg group had co-amoxiclav MICs of 8 mg/L. Although the number of PRSP strains isolated was small, the data support the results of recent animal models of respiratory tract infection, using simulated human pharmacokinetics, in which co-amoxiclav 2000/125 mg was demonstrated to be efficacious against *S. pneumoniae* with co-amoxiclav MICs of 8 mg/L.12,23

In addition, this study supports an analysis of 10 clinical studies of pharmacokinetically enhanced co-amoxiclav in CAP, acute exacerbations of chronic bronchitis and sinusitis.24 In this analysis, co-
amoxiclav 2000/125 mg had high therapeutic success in patients with *S. pneumoniae* infections (94.6%), including 51/52 (98.1%) with PRSP isolates and 14/15 (93.3%) with PRSP isolates with elevated co-amoxiclav MICs (≥4 mg/L).24

It is possible that in areas of increased prevalence of PRSP, the introduction of therapy with co-amoxiclav 2000/125 mg could delay or reduce the risk of further increases in the prevalence of penicillin-resistant pneumococci, as has been demonstrated in a study of the use of high-dose, short-course (5–7 days) amoxicillin in children.25

Both co-amoxiclav formulations in the current study were well tolerated, and co-amoxiclav 2000/125 mg had a safety profile consistent with that of existing formulations. The twice-daily regimen of the new formulation of co-amoxiclav has the potential to improve treatment compliance compared with the three-times-daily regimen of co-amoxiclav 875/125 mg.

In conclusion, co-amoxiclav 2000/125 mg twice daily was at least as efficacious clinically as co-amoxiclav 875/125 mg three times daily in the treatment of adult patients with CAP, and was generally well tolerated. Although the number of PRSP isolated in this study was low, the pharmacokinetically enhanced formulation effectively treated 3/3 patients with PRSP infection, including isolates with elevated co-amoxiclav MICs. This is in line with other studies of co-amoxiclav 2000/125 mg.21,26–28 Taken together, these studies suggest that the new formulation of co-amoxiclav is of great potential benefit in the empirical treatment of CAP and may be a valuable alternative therapy for patients in areas with a high prevalence of PRSP.

<table>
<thead>
<tr>
<th>Table 5. Frequency of adverse events with suspected or probable relationship to study medication (reported by ≥1% of patients in the ITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event</strong></td>
</tr>
<tr>
<td>Patients with ≥1 adverse event with suspected or probable relationship to study medication</td>
</tr>
<tr>
<td>Diarrhoea</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Pneumonia</td>
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<tr>
<td>Dyspepsia</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Hepatic enzymes increased</td>
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<td>Genital candidiasis</td>
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<tr>
<th>Table 6. Frequency of adverse and other complicating events leading to withdrawal from study (on-therapy and within 30 days post-therapy) in the ITT population</th>
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</thead>
<tbody>
<tr>
<td><strong>Event</strong></td>
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<tr>
<td>Patients with ≥1 adverse event leading to withdrawal</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Pulmonary carcinoma</td>
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<tr>
<td>Hepatitis cholestatic</td>
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<tr>
<td>Overdose</td>
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<tr>
<td>Urticaria</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Embolism, pulmonary</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Moniliasis genital</td>
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<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Vomiting</td>
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Co-amoxiclav 2000/125 mg twice daily in CAP

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