2. Synopsis

Abbreviated Clinical Study Synopsis:
Study B3M-GH-S027

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Title of Study: Cefaclor RTU versus Amoxicillin/Clavulanate in Acute Bacterial Lower Respiratory Tract Infections in Children

Investigators: This multicenter study included 5 principal investigators.

Study Centers: This study was conducted at 5 study centers.

Publication(s) Based on the Study: None at this time.

Length of Study: 12 months
- Date of first patient enrolled: 10 September 2001
- Date of last patient completed: 18 September 2002

Phase of Development: IV

Objectives: The primary objective of this study was to compare the therapeutic effects of cefaclor RTU (Ready to Use) (40 mg/kg given in two divided doses) administration for 10 days with that of amoxicillin/clavulanate (45 mg/kg given in two divided doses) administration for 10 days in the treatment of acute lower respiratory tract infection (LRTI) in children.

The secondary objectives of the study were:
- To determine the safety profiles of cefaclor RTU (40 mg/kg given in two divided doses) administration and amoxicillin/clavulanate (45 mg/kg given in two divided doses) for the 10-day treatment of LRTI in children.
- To compare the gastrointestinal (GI) tolerability of cefaclor RTU (40 mg/kg given in two divided doses) and amoxicillin/clavulanate (45 mg/kg given in two divided doses) for the 10-day treatment of LRTI.

Methodology: This was a randomized, parallel, single-blind (investigator-blinded), multicenter study.

Number of Patients:
- Planned: 110 cefaclor RTU, 110 amoxicillin/clavulanate
- Randomized: 110 cefaclor RTU, 110 amoxicillin/clavulanate
- Completed: 102 cefaclor RTU, 97 amoxicillin/clavulanate

Diagnosis and Main Criteria for Inclusion: Subjects included in the study had been diagnosed with an LRTI including acute bacterial bronchitis or mild pneumonia. The age range of the patients recruited was 6 months to 3 years 11 months, the weight range was 6 to 22 kg and there were 132 males and 88 females.

Test Product, Dose and Mode of Administration, Batch Number: Cefaclor RTU: 40 mg/kg/day, given in two divided doses.

Duration of Treatment: 10 days

Reference Therapy, Dose and Mode of Administration, Batch Number: Amoxicillin/clavulanate: 45 mg/kg/day, given in two divided doses.
### Criteria for Evaluation:

**Efficacy:** Evaluation of severity of signs and symptoms of infection, laboratory and bacteriology tests, and chest x-rays  
**Safety:** Recording and evaluation of clinical adverse effects and solicited GI events  
**Statistical Methods:** A Chi-squared test was carried out to compare the proportion of patients whose symptomatic response was either cured or markedly improved at the end of the study.
Summary and Conclusions:
This study enrolled 220 patients, with 110 patients randomized to the cefaclor RTU arm and 110 patients randomized to the amoxicillin/clavulanate arm. The patients had acute bronchitis (61.4% overall; 59.1% of the cefaclor arm, 63.6% of the amoxicillin/clavulanate arm) or pneumonia (38.6% overall; 40.9% of the cefaclor arm, 36.4% of the amoxicillin/clavulanate arm). Eight patients discontinued the study due to an adverse event (4 from the cefaclor group, 4 from the amoxicillin/clavulanate group), 1 patient discontinued due to patient perception of lack of efficacy (from the amoxicillin/clavulanate group), 4 patients discontinued due to physician perception of lack of efficacy (1 from the cefaclor group, 3 from the amoxicillin/clavulanate group) and 8 patients discontinued due to a patient decision (3 from the cefaclor group, 5 from the amoxicillin/clavulanate group). All analyses presented here are for the intent-to-treat population.

The response rates to cefaclor RTU and amoxicillin/clavulanate treatment are summarized in Table 1. Both regimens were effective in treating LRTIs, with the most common symptomatic response in both arms being Markedly Improved, followed by Cure. There appeared to be similar proportions of patients who failed, improved, markedly improved and were cured in the two treatment arms. When the responses were classified as Success (Cure or Markedly Improved) or Failure (Improvement or Failure), 85.5% of patients in the cefaclor group (95% CI = 78.9%-92.0%) and 82.7% of patients in the amoxicillin/clavulanate group (95% CI = 75.7%-89.8%) were successfully treated (Table 2). The response rates for the two treatment arms were not significantly different (p=0.580).

For each of the symptoms examined (cough, wheeze, pulmonary rales, aspiration withdrawal, tachynea and fever), the change in respiratory infection status from baseline to endpoint (improve, no change or worse) was summarized for each treatment group and is shown in Table 3. There appeared to be little difference between the two groups in the effect of treatment on the signs and symptoms of infection. Cough and pulmonary rales were improved in the majority of patients and most patients showed no change or an improvement in wheeze, aspiration withdrawal, tachynea and fever. Only a small number of patients experienced a worsening in any of these symptoms. For each symptom the relevant population was subdivided into patients with and without symptoms at baseline. For patients with symptoms at baseline, the endpoint outcome (improve or not improve) is shown in Table 4. For patients with no symptoms at baseline, the endpoint outcome (absent or present) has been summarized for each treatment group in Table 5. There were no significant differences between the two groups for either analysis. For patients with symptoms at baseline, the majority of patients in both treatment groups showed an improvement in all symptoms with only a few patients not improving in each category, apart from the aspiration withdrawal category in which all of the patients improved (Table 4). For patients with no symptoms at baseline, the majority of patients in both groups remained without symptoms. Only a small number of patients developed symptoms in each category except cough (all patients had cough at baseline) and pulmonary rales (no patient developed pulmonary rales) (Table 5).

Adverse events are shown in Table 6. The only significant difference between the two treatment groups was for pyrexia: 6 patients from the cefaclor group, but none from the amoxicillin/clavulanate group, discontinued the study because of pyrexia.
GI tolerance of the two treatment regimes was examined by monitoring nausea, vomiting, diarrhea and abdominal pain. Table 7 shows the maximum severity of these symptoms at Visit 2 or Visit 3 (post-therapy). Most patients did not experience any of these symptoms, indicating that both treatments were well tolerated. The symptoms that were reported were mostly classified as mild or moderate with only 2 reports of severe symptoms (both diarrhea in the amoxicillin/clavulanate group). For each of the GI symptoms, the change in tolerance from baseline to endpoint (improve, no change or worse) was summarized for each treatment group and is shown in Table 8. Most patients experienced no change in any of these symptoms, with only a small percentage of patients experiencing a worsening in any of the symptoms.

Sputum bacterial cultures were performed pre-therapy (Visit 1) and post-therapy (Visit 3) and the microorganisms that were identified are presented in Table 9 and Table 10, respectively. The most prevalent organisms in both treatment arms pre-therapy were *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. Following cefaclor or amoxicillin/clavulanate treatment considerably fewer patients were found to be harboring these pathogens. The antibiotic resistance of the isolated microorganisms to cefaclor was determined pre- and post-therapy (Tables 11 and 12). Comparison of these two tables shows that in the cefaclor group there were similar numbers of patients with *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* microorganisms resistant to cefaclor before and after treatment, indicating that cefaclor treatment is not associated with increased antibiotic resistance to cefaclor.

Both cefaclor RTU and amoxicillin/clavulanate were found to be effective in treating LRTIs in children in this study. There was very little difference observed between the two treatments; both treatments had a high response rate, improved the symptoms of infection and were safe with good GI tolerability.