FINAL REPORT SYNOPSIS

TITLE OF STUDY: A Randomized, Investigator-Blinded, Multicenter, Comparative Study of Cefprozil Versus High-Dose Amoxicillin/Clavulanate in the Treatment of Otitis Media in Children

INVESTIGATORS: 20 investigators were recruited and 15 enrolled patients in the U.S.

STUDY CENTERS: 20 Study sites were recruited and 15 enrolled patients in the U.S.

PUBLICATIONS: None.

STUDY PERIOD: Date first subject enrolled: 17-Mar-2000
Date last subject completed: 22-May-2000

CLINICAL PHASE: IV

OBJECTIVES: To assess whether the clinical efficacy of cefprozil is not inferior to that of high-dose amoxicillin/clavulanate based on the clinical cure rate at 4 to 7 days post-treatment in children aged six months up to and including seven years with otitis media.

METHODOLOGY: Randomized, investigator-blinded, multicenter, comparative study.

NUMBER OF SUBJECTS/PATIENTS: Total enrollment was 304 patients; 303 were treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Children six months up to and including 7 years of age with one or more of the local signs and symptoms consistent with otitis media: ear pain or ear ache (includes tugging or rubbing of ear), ear fullness, discharge from external canal or decreased hearing. Also, one or more of the following otoscopic findings: bulging tympanic membrane, which may be erythematous, loss of the normal light reflex and tympanic membrane landmarks or abnormal tympanic membrane mobility on pneumatic otoscopy due to the presence of pus or fluid behind the membrane and edema of the membrane.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Cefprozil oral suspension (Batch No. 9L12389) given orally, 15 mg/kg BID.

DURATION OF TREATMENT: Ten consecutive days.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Amoxicillin and amoxicillin/clavulanate oral suspension (Batch No. MK2534 and MK2509, respectively) given orally, 45/3.2 mg/kg BID.

CRITERIA FOR EVALUATION:

Efficacy: Clinical responses were determined from the data at the Test of Cure Visit scheduled between Day +4 to Day +7, inclusive. In the analysis, due to the potential schedule conflicts, any visit from Day +3 to Day +10, inclusive, was acceptable. Treatment failures could be assessed earlier, but these patients had to receive a minimum of three days of therapy to be considered evaluable for the primary efficacy analysis.

Safety: Safety data was collected between the first day of study drug treatment and 30 days after the last day of study drug treatment. Variables included deaths, adverse clinical events and serious adverse clinical events.
STATISTICAL METHODS: Data Sets - There were three study populations of interest:

- **All Treated Patients**: All patients who received at least one dose of study medication. This population was used to assess safety of the study regimens.
- **Eligible Patients**: All treated patients who met the diagnosis of acute otitis media at entry as defined by:
  - Two or fewer episodes of otitis in the previous six months excluding current episode;
  - One or more of the following local signs and symptoms consistent with otitis media;
    - ear pain or earache (includes tugging or rubbing of ear),
    - ear fullness,
    - discharge from external canal,
    - decreased hearing.
  - One or more of the following pneumatic otoscopic findings:
    - bulging tympanic membrane, which may be erythematous (a red tympanic membrane alone is inadequate),
    - loss of the normal light reflex and tympanic membrane landmarks,
    - abnormal tympanic membrane mobility on pneumatic otoscopy due to the presence of pus or fluid behind the membrane and edema of the membrane.
  - Six months up to and including 7 years of age at the time of enrollment.

This population was used in secondary analyses of efficacy.

- **Clinically Evaluable Patients**: All eligible patients who met the following criteria:
  - Received at least 6 doses of study medication appropriately administered (i.e., 6 doses of cefprozil or 6 doses of both amoxicillin and amoxicillin/clavulanate) but no more than 24 doses of study medication;
  - Had a Test of Cure Assessment (Day +4 to Day +7 post-treatment visit);
  - Received no systemic antibacterial with documented (e.g., in the package insert) activity against the most common respiratory pathogens for an infection other than otitis media prior to the Test of Cure.

This population was used in the primary efficacy analysis.

EFFICACY RESULTS: Clinical cure was recorded for 110 (87%) of 127 clinically evaluable patients given cefprozil and for 116 (89%) of 130 evaluable patients given high-dose amoxicillin/clavulanate [95% confidence interval for the difference in response rates: (-10.7%, 4.1%)]. The two regimens were comparable regardless of infection severity, age (younger than 2 years vs 2 and older), or type of infection (unilateral vs. bilateral).

SAFETY RESULTS: The overall incidence of any adverse clinical event was similar in the two groups (54% cefprozil, 55% high-dose amoxicillin/clavulanate). Drug-related adverse events occurred more frequently with amoxicillin/clavulanate compared with cefprozil (P = 0.008). Amoxicillin/clavulanate was associated with higher frequencies of diarrhea (P = 0.021), rash, and vomiting, the most common adverse events. Four patients given cefprozil (3%) and 8 patients given high-dose amoxicillin/clavulanate (5%) were discontinued from the study because of adverse clinical events.
CONCLUSIONS: Ten-day regimens of cefprozil 15 mg/kg twice daily and high-dose amoxicillin/clavulanate 45/3.2 mg/kg twice daily had equivalent clinical efficacy in children with acute otitis media. Cefprozil was better tolerated and caused fewer drug-related adverse events or treatment discontinuations.

DATE OF REPORT: 22-Dec-2000