2. Synopsis

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Clinical Study Synopsis: Study B9U-MC-AZCR

Title: Loracarbef in Pediatric Patients with Skeletal Infections

Investigators: This study included one principal investigator.

Study Centers: There was one study center.

Dates of Study: January 1996 through July 1997

Clinical Phase: Phase IIIb

Objectives: The primary objective was to evaluate the efficacy of loracarbef in a dose of 75 to 125 mg/kg/day in three divided doses, following a treatment regimen of intravenous antibiotics (cefoxime or another agent to cover suspected or documented pathogens) for treatment of septic arthritis and/or osteomyelitis in infants and children ages 6 months to 15 years.

The secondary objective was to evaluate the safety profile in this same group of patients.

The tertiary objective was to determine the peak and trough levels of loracarbef in this same group of patients.

Methodology: Open-label and non-comparative.

Number of Subjects: Loracarbef: Male 13, Female 11, Total 24;

Diagnosis: Acute osteomyelitis 16, Acute septic arthritis 8.

Diagnosis and Inclusion Criteria: Patients 6 months to 15 years who had signed or whose parents/guardian had signed an approved informed consent document. The patient must have had a diagnosis of acute septic arthritis and/or osteomyelitis and initial therapy with intravenous antibiotics. For the purposes of this study, patients with septic arthritis and/or osteomyelitis were defined by presence of at least 2 of the following clinical signs and symptoms: bone pain; fever; joint swelling; redness; tenderness; reduced range of motion.

In addition, qualified patients must have had one of the following: 1) presence of turbid synovial fluid with elevated leukocyte count (generally > 20,000/mm³); predominantly polymorphonuclear differential count; elevated protein concentration, 2) bone pus with positive culture or
demonstration of bacteria on Gram stain. 3) positive blood culture, 4) evidence of infection by MRI, bone scan or CT scan, 5) elevated sedimentation rate.

Dosage and Administration: Began Loracarbef therapy at 75-100 mg/kg/day and adjusted up to 125 mg/kg/day to achieve peak bactericidal concentrations of at least 1:8 versus the pathogen identified at admission (or standard laboratory Staphylococcus aureus strain).

Duration of Treatment: Loracarbef: 3-6 weeks.

Criteria for Evaluation: Efficacy-- Clinical improvement was defined as resolution of signs and symptoms (i.e. bone pain; fever; and joint swelling, redness, tenderness, and improvement in range of motion). Laboratory data indicating improvement consisted of reduction in sedimentation rate, C-reactive protein and leukocyte count. Follow-up examinations were performed at approximately one week intervals until clinical and laboratory markers were normal and then at one and six months after discontinuation of loracarbef therapy for all patients.

Safety-- The investigator was responsible for monitoring the safety of patients who entered this study and for alerting Lilly to any event that seemed unusual.

Statistical Methods: Descriptive statistics were reported for patient characteristics, safety and efficacy results.

Summary and Conclusions: This study was a single site open, prospective, noncomparative, therapeutic trial of high dose oral loracarbef in follow-up of standard parenteral treatment of bacterial osteomyelitis/septic arthritis in pediatric patients. Twenty-four patients, 16 with osteomyelitis and 8 with septic arthritis, were enrolled in the study. Patients with clinical signs and symptoms (fever, pain, swelling, erythema, and/or elevated sedimentation rate) of musculoskeletal infection were worked up with blood, bone and/or joint cultures as indicated and placed on parenteral antibiotic treatment with either cefuroxime or cefazolin. Of the 24 patients enrolled in the study, 14 had culture(s) positive for an organism known to cause blood borne infection of the bone or joint. Nine (9) cultures were positive for Staphylococcus aureus, four (4) for Streptococcus pyogenes and one (1) for Streptococcus pneumoniae. Patients were on parenteral therapy from 4 to 12 days (mean=7.7days) before being switched to oral loracarbef treatment with 75 to 100 mg/kg/day of the suspension divided TID. The dose of loracarbef was adjusted up to 125 mg/kg/day to achieve a peak serum bactericidal dilution titer of 1:8 or greater for the isolated organism. For culture negative infections, a laboratory strain of Staphylococcus aureus was used as the indicator bacteria. Patients were treated with oral loracarbef for 11 to 120 days with a mean of 30 days based on resolution of their inflammatory signs and symptoms. Peak serum concentrations of loracarbef achieved with oral doses of 90 to 125 mg/kg/day ranged from 11.04 to 49.06 ug/ml with adequate serum bactericidal titers for the relevant organism. All infected patients were clinically cured with this regimen. Sixteen (16) patients reported at least one adverse event over the term of the study most commonly gastrointestinal related complaints. However, without a placebo or comparator and given the length of the study this rate is probably within the expected range.

Conclusion: High dose (>75mg/kg/day) of oral loracarbef suspension appears to be adequate follow-up treatment of musculoskeletal infections in children. These doses result in high peak plasma levels with bactericidal titers adequate to treat most infecting organisms.