SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Zevtera™; Zeftera™
Name of Active Ingredient(s)	ceftobiprole

Protocol No.: CEFTO-NOS-1002

Title of Study: Open-Label, Exploratory, Multiple-Dose Study of Ceftobiprole to Evaluate the Pharmacokinetics and Broncho Alveolar Penetration in Adults with Ventilator-Associated Pneumonia

NCT No.: NCT00771719

Clinical Registry No.: CR015304

Study Centers: Multicenter study at sites in the United States, Spain, and Republic of Korea.

Publication (Reference): None

Study Period: 2 October 2008 to 16 November 2009

Phase of Development: Phase 1

Objectives: The primary objective was to assess the steady-state pharmacokinetics of ceftobiprole 1000 mg when administered every 8 hours as a 4-hour infusion in subjects with VAP and to evaluate the penetration of ceftobiprole into the epithelial lining fluid (ELF) and alveolar macrophages in the lung.

The secondary objective was to evaluate the safety of ceftobiprole when administered as this regimen in subjects with VAP.

Hypothesis: A higher dose of 1000 mg and a longer infusion duration of 4 hours should provide greater concentrations of ceftobiprole in the systemic circulation and greater %T>MIC in plasma of VAP subjects, compared with the currently recommended dosing regimen for cSSSI of 500 mg every 8 hours, administered as a 2-hour infusion. With greater systemic exposure, concentrations in the ELF are expected to be higher in VAP subjects compared with those observed historically in healthy subjects. This was an estimation study and no formal statistical analysis was planned

Methodology: This was a multi-center, open-label, exploratory, multiple-dose, study in adults with VAP. The study had 3 phases: a 24-hour screening phase; a 2-day open-label treatment phase, with end-of-study/early withdrawal procedures on Day 3 and a follow-up assessment approximately 1 week after dosing, to evaluate new and ongoing adverse events. The total duration of the study was approximately 9 days, including screening and post-treatment. The inclusion and exclusion criteria for the study were defined in the study protocol.

Twenty-two subjects (20 active and 2 control) with VAP were planned to be included in the study. The 2 control subjects were to receive no ceftobiprole; they were to undergo the broncho alveolar lavage (BAL) procedure only. These control samples were to be used to qualify the bioanalytical assay using the BAL fluid. The remaining 20 subjects were to receive a total of four doses of ceftobiprole 1000 mg, administered as a 4-hour intravenous infusion every 8 hours. Blood samples were to be collected for estimation of ceftobiprole pharmacokinetics according to the Time and Events Schedule in the protocol. A single bronchoscopy and BAL sample was to be collected at either 4 hours (n=10) or 8 hours (n=10) after the start of the fourth infusion.

This study included the following evaluations of ceftobiprole safety and tolerability: adverse events; clinical laboratory tests including hematology, serum chemistry, and urinalysis; vital signs, measurements, including oral temperature (or equivalent), pulse, respiratory rate, and blood pressure; and physical examinations.

Results: During the 13-month enrollment period, the sponsor had discussions with all participating investigators and reviewed the screening logs. The investigators identified significant enrollment challenges in the target subject population (patients diagnosed with VAP). Based on this feedback, the lack of consistent screening activity, and poor enrollment, the study was terminated.

At the time the study was terminated, 1 control subject had been enrolled and completed the study. This subject, who only underwent the BAL procedure and did not receive ceftobiprole, did not report any adverse events. No other subjects were enrolled.

Study Limitations and Conclusions No conclusions could be drawn from this study because the study was terminated for administrative reasons after only 1 control subject had been enrolled.

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