

Single Oral Dose Pharmacokinetics and Safety of CEM-101 in Healthy Subjects

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Background:

CEM-101 is a potent new ketolide currently under development for treatment of respiratory tract infections. CEM-101 pharmacokinetics and safety following escalating single oral doses administered under fasting conditions were investigated in this first-in-human study.

Methods:

This was a Phase 1, randomized, double-blind, placebo-controlled, dose escalation study. Escalating single doses (50, 100, 200, 400, 800, 1200, and 1600 mg) were administered to seven groups of healthy adult subjects using 50, 100, or 200 mg CEM-101 or matching placebo capsules. Within each dose group, 5 subjects received CEM-101 and 2 received placebo. Dose escalation proceeded only after the safety of the previous dose was determined. Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events (AEs) were monitored throughout the study. Blood samples for assay of CEM-101 concentrations and pharmacokinetic assessment were collected pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post-dose.

Results:

Over the dose range studied, the mean CEM-101 $T_{1/2}$ ranged from 2.2 to 7.9 h. The median T_{max} increased from 1.5 h at 50 mg to 6 h at 1600mg. The mean C_{max} and AUC_{0-inf} ranged from 22.3ng/mL and 81.5 ng•h/mL to 1970 ng/mL and 28900 ng•h/mL over the dose range. The C_{max} and AUC_{0-inf} increases were more than proportional across the dose range. These doses of CEM-101 were safe and generally well tolerated. AEs were reported in 12 of the 49 (24%) study subjects, all mild or moderate in severity. The most common AE was headache, occurring in 9 subjects. Nausea and/or diarrhea were seen in 2 subjects in the 1200 and 1600 mg dose cohorts, suggesting possible gastrointestinal intolerance beginning at these doses.

Conclusions:

Over the 50 mg to 1600 mg dose range, CEM-101 was safe and generally well tolerated in healthy male and female subjects. C_{max} and AUC_{0-inf} increases were more than dose proportional across the dose range administered.