

Multiple Dose Pharmacokinetics and Safety of CEM-101, a New Fluoroketolide, in Healthy Subjects

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Objectives: CEM-101 is a potent new fluoroketolide under development for the treatment of bacterial respiratory tract infections. CEM-101 pharmacokinetics (PK) and safety at single doses up to 1600 mg have been reported previously. Safety and PK following escalating multiple oral doses were investigated in this study.

Methods: This was a randomized, double-blind, placebo-controlled, dose escalation study. Escalating doses (200, 400, and 600 mg) were administered once daily for 7 days to healthy adult subjects (5:2, active: placebo; 200 mg [n=7], 400 mg [n=14] and 600 mg [n=14]). Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events were monitored throughout the study. Blood samples for CEM-101 concentrations and PK assessments were collected pre-dose and at frequent intervals to 24 h post-dose on Day 1 and to 72 h post-dose on Day 7.

Results: CEM-101 mean C_{\max} values on Days 1 and 7 were 0.113 and 0.248 $\mu\text{g}/\text{mL}$ for the 200 mg group, 0.579 and 1.09 $\mu\text{g}/\text{mL}$ for the 400 mg groups, and 0.862 and 1.50 $\mu\text{g}/\text{mL}$ for the 600 mg groups. Corresponding $\text{AUC}_{(0-24)}$ values on Days 1 and 7 were 0.888 and 2.31 $\mu\text{g}\cdot\text{h}/\text{mL}$, 4.85 and 13.30 $\mu\text{g}\cdot\text{h}/\text{mL}$, and 7.64 and 18.40 $\mu\text{g}\cdot\text{h}/\text{mL}$. Increases in C_{\max} and $\text{AUC}_{(0-24)}$ were more than dose proportional from 200 to 400 mg and then approximately dose proportional from 400 to 600 mg. At all doses CEM-101 exposures were higher on Day 7 than Day 1, indicating that accumulation occurred over the dosing period. Across the doses the mean T_{\max} ranged from 3.0 to 4.0 hours, and the mean $T_{1/2}$ increased from 3.64 to 5.45 hours on Day 1 and from 5.39 to 8.07 hours on Day 7. All doses of CEM-101 were safe and generally well tolerated. Gastrointestinal AEs, mostly mild, occurred in each dose group. Low-level hepatic transaminase increases occurred in 4 of 10 subjects that received 600 mg CEM-101; all were transient, reversible, and not associated with signs or symptoms of toxicity.

Conclusion: Over the 200 to 600 mg dose range, multiple doses of CEM-101 were safe and well tolerated in healthy adult subjects. C_{\max} and AUC increases were more than dose proportional from 200 to 400 mg, and approximately dose proportional from 400 to 600 mg. CEM-101 showed moderate accumulation over 7 days of dosing.