Pharmacokinetics and Safety of Single, Multiple, and Loading Doses of CEM-102 in Healthy Subjects.

J.G. STILL[1], K. CLARK[1], T.P. DEGENHARDT[1], D. SCOTT[1], P. FERNANDES[1], M.J. GUTIERREZ[2]

[1]Cempra Pharmaceuticals, Inc., Chapel Hill, NC, [2]Comprehensive Phase One, Miramar, FL

Background:

CEM-102 is a fusidane class antibiotic under development for treatment of gram-positive complicated skin and skin structure infections. PK and safety of escalating single (SD), multiple (MD) and loading dose (LD) regimens of oral CEM-102 were evaluated.

Methods:

This was a randomized, double-blind, placebo-controlled, dose escalation study. CEM-102 doses (550, 1100, 1650, 2200 mg) were administered as SD, then BID for 5.5 days to 4 groups of healthy subjects in the fasting state. In addition, 2 LD regimens (1100 or 1650 mg BID on Day 1 followed by 550 or 825 mg BID for 6.5 days) were evaluated. In each group 6 subjects received CEM-102 and 2 received placebo. Dose escalation occurred after safety of the previous dose was determined. Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events (AEs) were monitored. Blood for assay of CEM-102 concentrations and PK analysis was collected pre-dose and at specified intervals after each dose.

Results:

Mean C_{max} and AUC_{0-t} ranged from 33.4 µg/mL and 242 µg▪h/mL to 128 µg/mL and 1690 µg▪h/mL for SD of 550 to 2200 mg and from 130 µg/mL and 1150 µg▪h/mL to 324 µg/mL and 3290 µg▪h/mL for MD of 550 to 1650 mg. LD regiments resulted in trough concentrations on Days 2 and 8 of 73.8 and 101 µg/mL (1100/550 mg regimen) and 146 and 204 µg/mL (1650/825 mg regimen). All doses appeared to be safe. SD up to 1650 mg, MD up to 1100 mg BID, and both LD regimens were well-tolerated. Nausea and vomiting occurred at SD 2200 mg (1 subject) and MD 1650 (4 subjects), therefore MD above 1650 mg were not administered. No other clinically meaningful AEs were seen. There were no clinically significant changes in monitored safety parameters.

Conclusions:

CEM-102 was safe at all doses. Plasma exposure was higher after MD compared to SD, indicating accumulation with MD. LD regimens were well-tolerated and produced plasma concentrations that approached steady-state at 24 hours.