Study Design

Objectives: To determine the safety and tolerability of multiple escalating doses of oral CEM-101. Clinical pharmacokinetics (PK) and safety at single doses up to 1,600 mg and at multiple doses up to 600 mg CEM-101 are evaluated. CEM-101 was not mutagenic or clastogenic. In vitro, CEM-101 inhibited the anchorage-dependent growth of HeLa cells. CEM-101 is highly active against common bacterial respiratory tract infection pathogens (S. pneumoniae, H. influenzae, L. pneumophila, and M. tuberculosis) as well as atypical bacteria (M. pneumoniae, C. pneumoniae, and L. pneumophila). CEM-101 is highly active against common bacterial respiratory tract infection pathogens (S. pneumoniae, H. influenzae, L. pneumophila, and M. tuberculosis) as well as atypical bacteria (M. pneumoniae, C. pneumoniae, and L. pneumophila). CEM-101 demonstrates potent bactericidal activity against macrolide-resistant pneumococci (S. pneumoniae), atypical pneumococci (S. pneumoniae), and H. influenzae (S. pneumoniae, H. influenzae). CEM-101 exhibited excellent activity (MIC90 ≤ 0.03 µg/mL) against the following bacteria: S. pneumoniae, H. influenzae, L. pneumophila, and M. tuberculosis. CEM-101 also inactivated CYP3A4 in kinetic studies. As both a substrate for, and inhibitor of CYP3A4, CEM-101 may interact with other drugs that are metabolized by CYP3A4, and may have clinically significant interactions with drugs that are substrates or inhibitors of CYP3A4.

Subjects

CEM-101 was safe and generally well tolerated in healthy male and female adult subjects orally administered 7 daily doses of 250 mg, 400 mg, and 600 mg. Low-level serum transaminase elevations were observed in 4 subjects administered 800 mg CEM-101; levels returned rapidly to normal after dosing was completed. CEM-101 was not mutagenic or clastogenic. In vitro, CEM-101 inhibited the anchorage-dependent growth of HeLa cells. CEM-101 is highly active against common bacterial respiratory tract infection pathogens (S. pneumoniae, H. influenzae, L. pneumophila, and M. tuberculosis) as well as atypical bacteria (M. pneumoniae, C. pneumoniae, and L. pneumophila). CEM-101 demonstrates potent bactericidal activity against macrolide-resistant pneumococci (S. pneumoniae), atypical pneumococci (S. pneumoniae), and H. influenzae (S. pneumoniae, H. influenzae). CEM-101 was not mutagenic or clastogenic. In vitro, CEM-101 inhibited the anchorage-dependent growth of HeLa cells. CEM-101 also inactivated CYP3A4 in kinetic studies. As both a substrate for, and inhibitor of CYP3A4, CEM-101 may interact with other drugs that are metabolized by CYP3A4, and may have clinically significant interactions with drugs that are substrates or inhibitors of CYP3A4.

Conclusions

The mean PK results for CEM-101 in plasma for Cohorts A-E are shown as descriptive statistics in Table 1, and the mean plasma concentrations of CEM-101 for each cohort are depicted in a linear plot in Figure 1. Across the doses studied, the mean Cmin and AUC0-24 ranged from 0.11 and 0.25 µg/mL and 0.96 and 2.31 µg*h/mL (respectively, on Day 7) for 200 mg and 0.50 and 1.56 µg/mL and 1.08 and 17.60 µg•h/mL for the 600 mg dose. Increases of Cmax and AUC0-24 were more than dose proportional from 200 mg to 400 mg and approximately dose proportional from 400 mg to 600 mg. At all doses, safety assessments were higher on Day 7 than on Day 1, indicating that accumulation occurred over the dosing period. The mean T2/2 was 3.0 h. Across the doses studied, the mean Cmin and AUC0-24 ranged from 0.11 and 0.25 µg/mL and 0.96 and 2.31 µg•h/mL (respectively, on Day 7) for 200 mg and 0.50 and 1.56 µg/mL and 1.08 and 17.60 µg•h/mL for the 600 mg dose. Increases of Cmax and AUC0-24 were more than dose proportional from 200 mg to 400 mg and approximately dose proportional from 400 mg to 600 mg. At all doses, safety assessments were higher on Day 7 than on Day 1, indicating that accumulation occurred over the dosing period. The mean T2/2 was 3.0 h. Across the doses studied, the mean Cmin and AUC0-24 ranged from 0.11 and 0.25 µg/mL and 0.96 and 2.31 µg•h/mL (respectively, on Day 7) for 200 mg and 0.50 and 1.56 µg/mL and 1.08 and 17.60 µg•h/mL for the 600 mg dose. Increases of Cmax and AUC0-24 were more than dose proportional from 200 mg to 400 mg and approximately dose proportional from 400 mg to 600 mg. At all doses, safety assessments were higher on Day 7 than on Day 1, indicating that accumulation occurred over the dosing period. The mean T2/2 was 3.0 h. Across the doses studied, the mean Cmin and AUC0-24 ranged from 0.11 and 0.25 µg/mL and 0.96 and 2.31 µg•h/mL (respectively, on Day 7) for 200 mg and 0.50 and 1.56 µg/mL and 1.08 and 17.60 µg•h/mL for the 600 mg dose. Increases of Cmax and AUC0-24 were more than dose proportional from 200 mg to 400 mg and approximately dose proportional from 400 mg to 600 mg. At all doses, safety assessments were higher on Day 7 than on Day 1, indicating that accumulation occurred over the dosing period. The mean T2/2 was 3.0 h.