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Poster Session VI
PK/PD of antifungals and miscellaneous antibacterials

PHARMACOKINETICS AND SAFETY OF LETERMOVIR, A NOVEL ANTI-HUMAN CYTOMEGALOVIRUS DRUG, IN RENALLY IMPAIRED PATIENTS

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Objectives: Letermovir, a novel anti-human cytomegalovirus (HCMV) drug with a unique mechanism of action, is being developed for the prevention of HCMV viremia and/or disease in transplant recipients with both oral and intravenous formulations. Although letermovir is primarily excreted unchanged into the feces and the excretion into the urine is negligible in humans, renal impairment can have an influence on liver function and consequently, also on the pharmacokinetics of letermovir. The objective of the present trial was to evaluate the pharmacokinetics, safety and tolerability of letermovir in renally impaired patients compared to healthy volunteers.

Methods: This was an open-label trial in 24 male and female subjects: 8 healthy subjects (estimated glomerular filtration rate (eGFR) >= 90 mL/min/1.73m^2), 8 moderate renally impaired subjects (eGFR 30-59 mL/min/1.73m^2), and 8 severe renally impaired subjects (eGFR < 30 mL/min/1.73m^2). Each subject received 120 mg oral letermovir once daily for 8 days. The group of healthy volunteers was matched to each of the other groups for age and body mass index (BMI). Least square means of the primary parameters were estimated and 90% confidence intervals (CIs) were calculated for each of the 2 renal impairment groups as a percentage of the reference healthy volunteer group for AUC_tau,ss and C_max,ss of letermovir (based on total and unbound plasma concentrations).

Results: Letermovir was generally safe and well tolerated. No related SAEs or discontinuations due to AEs were reported. No trends in safety laboratory parameters, vital signs, ECG, or physical examination were apparent for any of the subject groups. For subjects with moderate renal impairment, mean [90% CI] total AUC_tau,ss and C_ss,max were 1.92 [1.43-2.58] and 1.25 [0.87,1.82] fold higher compared to healthy subjects, respectively (2.15 and 1.41-fold for the unbound fraction). For subjects with severe renal impairment, mean total AUC_tau,ss and C_ss,max of letermovir were 1.42 [0.83,2.43] and 1.06 [0.75,1.51] fold higher compared to healthy subjects, respectively (1.81 and 1.35-fold for unbound fraction). Linear regression analysis showed only a weak association between renal function and letermovir clearance (R^2=0.0662 and 0.1861 for clearance of total and free letermovir, respectively), suggesting other factors may play a role in the observed differences in exposure.
Conclusion: Oral 120 mg letermovir once daily dosing for 8 days was generally safe and well tolerated in subjects with moderate and severe renal impairment. Increases in total letermovir concentrations of up to 92% for AUC_tau,ss and 25% for C_ss,max were found in renally impaired patients compared to healthy volunteers.