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Paper Poster Session IV

Viral infection and disease

Pharmacokinetics and safety of letermovir, a novel drug against human cytomegalovirus, in hepatically 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. Both oral and intravenous formulations of Letermovir are being developed. In humans Letermovir is primarily excreted unchanged via bile into feces with the excretion into the urine being negligible. The objective of the present trial was to evaluate the pharmacokinetics, safety and tolerability of letermovir in hepatically impaired patients as compared to healthy volunteers.

Methods: This was an open-label trial in 32 female subjects (8 subjects per group): Group 1 were subjects with moderate hepatic impairment, Stage B according to Child-Pugh classification; Group 2 were healthy subjects individually matched for age ($\pm 10\%$), body mass index (BMI $\pm 10\%$), and the same ethnic origin of subjects as per Group 1; Group 3 were subjects with severe hepatic impairment, Stage C according to Child-Pugh classification; Group 4 were healthy subjects individually matched for age ($\pm 10\%$), body mass index (BMI $\pm 10\%$), and the same ethnic origin of subjects as per Group 3. Each subject received 60 mg (Groups 1 and 2) or 30 mg (Groups 3 and 4) oral letermovir once daily for 8 days to achieve steady-state concentrations of Letermovir. Least square means of the primary parameters were estimated and 90% confidence intervals (CIs) were calculated for each of the 2 hepatic impairment groups as a percentage of the respective reference healthy volunteer group for AUC_{tau,ss} and C_{ss,max} of letermovir (based on total and unbound plasma concentrations).

Results: For subjects with moderate hepatic impairment, mean [90% CI] total AUC_{tau,ss} and C_{ss,max} of letermovir were 1.59 [0.98-2.57] and 1.37 [0.87,2.17] fold higher compared to healthy subjects, respectively (1.81 and 1.56-fold for the unbound fraction). For subjects with severe hepatic impairment, mean total AUC_{tau,ss} and C_{ss,max} were 3.82 [2.94,4.97] and 2.34 [1.91,2.88] fold higher compared to healthy subjects, respectively (5.36 and 3.29-fold for unbound fraction). Letermovir was generally safe and well tolerated. No SAEs or discontinuations due to AEs were reported. There were no clinical relevant changes attributable to letermovir in safety laboratory parameters, vital signs, ECG, or physical examination in any of the groups.

Conclusion: Compared to healthy volunteers total letermovir concentrations were increased up to 59% for AUC_{tau,ss} and 37% for C_{ss,max} in moderate hepatically impaired patients and up to 282% for AUC_{tau,ss} and 134% for C_{ss,max} in severe hepatically impaired patients. Once daily oral 60 mg (Groups 1 and 2) or 30 mg (Groups 3 and 4) letermovir for 8 days was generally safe and well tolerated in subjects with moderate and severe hepatic impairment.