A population Pharmacokinetic Analysis of Telaprevir in Healthy Korean and Japanese Subjects

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Objectives: Telaprevir is a reversible selective inhibitor of viral protease and a potential blocker of viral replication, which is indicated for treatment of hepatitis C virus genotype 1 infection. The purpose of this study was to develop a population pharmacokinetic (PK) model of telaprevir in healthy Korean and Japanese subjects and to compare the PK characteristics between the two ethnic groups.

Methods: A population PK analysis was performed using 936 telaprevir concentrations in 42 subjects (24 Koreans and 18 Japanese), who received 500, 750 or 1250 mg of single-dose oral telaprevir in fasted state or 750 mg of multiple-dose oral telaprevir in fed state. Plasma concentrations of telaprevir were analysed using nonlinear mixed-effect modelling in NONMEM (ver 7.3). The first-order conditional estimation (FOCE) with interaction method was used to fit the plasma concentration-time data. Standard goodness-of-fit (GOF) diagnostics and visual predictive checks were used to evaluate the adequacy of the model fit and predictions.

Results: A one-compartment model using first-order absorption with lag time and proportional residual error best described the data. The typical population estimates of the apparent clearance (CL/F), volume of distribution (Vd/F), the absorption rate constant (Ka) and the lag time of absorption were 318 L/h, 789 L, 0.13 h⁻¹ and 0.21 h respectively. The inter-individual variabilities were 9.1 % for the CL/F and 11.3 % for the Vd/F. Food intake significantly increased Ka and relative bioavailability by 1.34- and 4.50-fold. Ethnicity had no statistically significant effect on the PK parameters. Model evaluation by GOF plot and VPCs indicated that the proposed model adequately described the data.

Conclusions: The population PK model for oral telaprevir was developed in healthy Korean and Japanese subjects, and the population PK parameters of telaprevir were not different between two ethnic groups.