Population Pharmacokinetic Analysis of ABT-493 Exposures in HCV-Infected Subjects

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Objectives: To characterize population pharmacokinetics of ABT-493, a nonstructural protein 3/4 A protease inhibitor discovered by AbbVie and Enanta, in HCV genotypes 1 to 6 subjects when co-administered with ABT-530, a nonstructural protein 5A inhibitor. Identify demographics, pathophysologic, and treatment factors that impact the exposure.

Methods: Plasma concentration samples from 641 subjects enrolled in 4 Phase 2 studies were analyzed using non-linear mixed-effects modeling using NONMEM 7.3. One, two and three compartment models were explored for structural model development. To characterize the greater than dose-proportional increase in ABT-493 exposure, a dose-dependent relative bioavailability was incorporated into the structural model. Both, categorical and continuous measures for demographics, pathophysiologic and treatment factors were tested for their effects on ABT-493 pharmacokinetics. Model evaluation and validation techniques were used to assess adequacy and robustness of the pharmacokinetic models.

Results: A two-compartment PK model with first-order absorption and elimination optimally described the ABT-493 concentration-time profile. The ABT-493 model-predicted concentration-time profile was comparable to the median (IPRED) profile of the observed data (Figure, left). A polynomial function fitted to the log-transformed AUC values was used to describe the non-linear dose-dependent increase in ABT-493 exposures (Figure, right). The identified sources of variability in the population pharmacokinetics were: body weight on volume of distribution (10% increase per 10 kg increase), and cirrhotic status on bioavailability (increased to 2.2 fold in cirrhotics). Genotype and ABT-530 dose were not significant factors. The population mean estimates (at the model’s reference covariate value) of ABT-493 CL/F was 1090 L/day and V2/F was 134 L.

Conclusions: The population pharmacokinetic model described the concentration-time profiles, as well as the non-linearity and variability of ABT-493 across ABT-493 doses, in HCV infected subjects with or without cirrhosis well. Genotype and ABT-530 dose have no impact on ABT-493 exposures.

Figure: Observed and Model-Predicted ABT-493 Concentration Versus Time (Time After Last Dose) Profile for 300/120 mg ABT 493/ABT 530 (Left) and Log-Transformed AUC Versus ABT-493 Dose (Right).

Left Panel: Gray circles: individual subject concentration; Black Circles and Error Bars: median of the observed binned concentrations and 5th and 95th percentile; Black Line (solid): model-predicted individual (IPRED) median concentration-time profile; Black Line (dotted): model-predicted population (PRED) median concentration-time profile.

Right Panel: Open blue circles and yellow triangles represent individual observed AUC values for non-cirrhotic and cirrhotic subjects, respectively. Filled blue circles and yellow triangles with error bars represent the median and 5th and 95th percentile of observed data for non-cirrhotic and cirrhotic subjects, respectively. Solid blue and yellow line represent the model fit for non-linearity for non-cirrhotic and cirrhotic subjects, respectively.