Population Pharmacokinetics of ABT-493 in HCV Genotype 1 Infected Subjects with or without Cirrhosis in Three-Day Monotherapy Study

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Objectives: ABT-493, an HCV nonstructural protein 3/4 A (NS3/4A) protease inhibitor discovered by AbbVie and Enanta, is under clinical development to be coadministered with ABT-530, a NS5A inhibitor, against HCV virus across genotypes 1 to 6. The objective of this analysis was to characterize population pharmacokinetics of ABT-493 in HCV genotype 1-infected subjects with or without cirrhosis in a three-day monotherapy study.

Methods: Population pharmacokinetic analysis was performed using data from 44 HCV infected subjects who received ABT-493 doses ranging from 100 to 700 mg QD (100, 200 (including cirrhotics), 300, 400, or 700 mg QD) following 3 day monotherapy. Population pharmacokinetic model was built using nonlinear mixed-effects modeling approach in NONMEM 7.3. Model evaluation and validation techniques were used to assess adequacy and robustness of the pharmacokinetic models.

Results: The observed pharmacokinetic profiles of ABT-493 exhibited delayed absorption and bi-phasic disposition. The delayed absorption was well described by a transit absorption model, and the bi-phasic disposition was well described by a two-compartment disposition model. The estimated mean transit time in absorption was 2.7 hr. The estimated apparent clearance (CL/F) and apparent volume of distribution (V/F) were 29 L/hr and 31 L, respectively. The concentration-time profiles of ABT-493 were adequately described by the final pharmacokinetic model as shown in Figure. Estimated relative bioavailability of ABT-493 increases with dose as the ABT-493 exposures increases in a higher than dose-proportional manner. Approximately 4.2-fold higher exposures of ABT-493 were observed in cirrhotic population compared to non-cirrhotic population.

Conclusions: The developed population pharmacokinetic model well described the concentration time profiles and variability of ABT-493 across wide ranges of ABT-493 doses in HCV infected subjects with or without cirrhosis. This population pharmacokinetic model can be used to conduct simulations to support selection of doses that achieve target exposures and to evaluate exposure-response relationships to inform combination therapy strategies.
Figure. Visual Predicted Check for ABT-493 population PK model