Population Pharmacokinetics of a Pangenotypic NS5A inhibitor, ABT-530, in HCV infected Patients with and without Cirrhosis : A Pooled Analysis from Phase 2 Studies

Aksana K. Jones1,*, Chih-Wei Lin1, Wei Liu1, Sandeep Dutta1

1Clinical Pharmacology and Pharmametrics, AbbVie

Objectives: ABT-530 in combination with ABT-493 is a novel 2 direct-acting antiviral agents (DAA) combination being developed for the treatment of HCV genotypes 1 to 6. The purpose of this analysis was to characterize the population pharmacokinetics of ABT-530 and explore demographics, pathophysologic, and treatment factors that may impact ABT-530 exposure.

Methods: Population pharmacokinetic models were built using nonlinear mixed-effects modeling approach in NONMEM 7.3. ABT-530 concentration data from 634 subjects from 4 Phase 2 studies were analyzed. Categorical and continous measures for demographics, pathophysiologic and treatment factors were tested for their effect on ABT-530 exposure. Model evaluation and validation techniques were used to assess adequacy and robustness of the pharmacokinetic models.

Results: Observed ABT-530 pharmacokinetic profile was well characterized by a two-compartment PK model with first-order absorption. An Emax function for relative bioavailability was used to characterize the dose-dependent non-linear increase in ABT-530 exposure (Figure, left) and the effect of ABT-493 on ABT-530 bioavailability. The identified sources of variability were sex on apparent clearance (21% higher in male) and body weight on apparent volume of distribution (9% increase per 10 kg increase). These effects on ABT-530 exposures were minimal and not clinically meaningful. Prediction corrected visual predictive checks indicated that the final model incorporating these covariates described the central tendency of the data well and the variability of the data adequately (Figure, right). The non-parametric bootstrap evaluation demonstrated good agreement with the estimated parameter values. The population mean estimates (at the model’s reference covariate values) of ABT-530 CL/F was 6520 L/day and V2/F was 1270 L.

Conclusions: The ABT-530 population pharmacokinetic model provided robust characterization of the observed ABT-530 exposures in HCV infected patients. None of the tested covariates have clinically meaningful impacts on ABT-530 exposure and do not require dose adjustment.

Figure: Log-transformed AUC Versus ABT-530 Dose (Left) and Prediction Corrected Visual Predictive Check (Right).

Left Panel: Open symbols represent individual observed AUC values, filled symbols with error bars representing the median and 5th and 95th percentile. Solid lines represent the model fit for non-linearity.

Right Panel: Open circles represent prediction corrected observed ABT-530 concentrations. The shaded gray area represents the 90% prediction interval of the prediction corrected simulated ABT-530 concentrations. The solid red line represents median, the dashed red lines represent the 5th and 95th percentile of the prediction corrected observed ABT-530 concentrations.