Population Pharmacokinetics of a Pangenetic NS5A inhibitor, ABT-530, in HCV infected Patients with and without Cirrhosis

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Objectives: ABT-530 is a nonstructural protein 5A (NS5A) inhibitor with pangenotypic activity against HCV virus. The purpose of this analysis was to characterize the population pharmacokinetics of ABT-530 in HCV infected subjects.

Methods: Data from 38 HCV infected subjects who received ABT-530 doses ranging from 15 to 400 mg QD (15, 40, 120 (with and without cirrhotics) or 400 mg QD) following 3 day monotherapy was included in the population pharmacokinetic analysis. The model was built using nonlinear mixed-effects modeling in NONMEM 7.3. Based on ABT-530 pharmacokinetic profile, transit compartments were explored to describe the delay in drug absorptions. A gamma density function was used to estimate the number of transit compartments during the model development. A schematic of the model is shown in Figure. Model evaluation and validations were conducted to assess adequacy and robustness.

Results: Observed ABT-530 pharmacokinetic profiles were well described by a two-compartment disposition model with a delayed absorption. Five transit compartments were estimated to describe the delayed absorption with a mean transit time of 4 hours, consistent with estimates from gamma density absorption function (4.6 transit compartments with a mean transit time of 3.6 hours) evaluated during model development. The estimated apparent clearance (CL/F) and apparent volume of distribution (V/F) were 300 L/hr and 220 L, respectively. The nonlinear pharmacokinetics of ABT-530 was addressed by dose-dependent bioavailability as elimination half-life was similar across doses. Both the observed exposures and the population pharmacokinetic model estimated exposures were similar in cirrhotic and non-cirrhotic subjects. Steady state exposures of ABT-530 are predicted to be achieved by Day 7 with minimal accumulation.

Conclusions: The developed ABT-530 population pharmacokinetic model well characterized the observed ABT-530 exposures in HCV infected patients and can be used in combination with viral response data to support dose selections and inform combination strategies. The gamma density function provided a fast and precise estimation of the number of transit compartments during model development.
Figure. Schematic of Population pharmacokinetic model

Transit Absorption with Two Compartment Disposition

Mean Transit Time (MTT) = \frac{N}{k_{tr}}

Transit compartments

\[
\frac{dA_1}{dt} = -\frac{1}{\tau} A_1 \\
\frac{dA_2}{dt} = -\frac{1}{\tau} A_1 - \frac{1}{\tau} A_2 \\
\vdots \\
\frac{dA_n}{dt} = \frac{1}{\tau} A_{n-1} - \frac{1}{\tau} A_n \\
\frac{dA_c}{dt} = \frac{1}{\tau} A_n - \frac{CL}{V_c} A_c - \frac{Q}{V_c} A_c + \frac{Q}{V_p} A_p \\
\frac{dA_p}{dt} = \frac{Q}{V_c} A_c - \frac{Q}{V_p} A_p
\]

Estimation of Number of Transit Compartments using Gamma Density Absorption

Input: \text{Gamma}(N, k_{tr})

\[
input(t, N, k_{tr}) = \frac{k_{tr}^N}{\Gamma(N)} t^{N-1} e^{-k_{tr}t}
\]

\[
\frac{dA_c}{dt} = input(t, N, k_{tr}) - \frac{CL}{V_c} A_c - \frac{Q}{V_c} A_c + \frac{Q}{V_p} A_p \\
\frac{dA_p}{dt} = \frac{Q}{V_c} A_c - \frac{Q}{V_p} A_p
\]