Viral Dynamics Modeling of MK-3682 Monotherapy in HCV-infected Patients

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Objectives: MK-3682 is a nucleoside analog inhibitor of the Hepatitis C Virus (HCV) Nonstructural protein (NS) 5B RNA polymerase. MK-3682 is being developed as one component of an all oral combination treatment regimen for treatment of chronic hepatitis C virus infection. We aim to investigate the antiviral effect of MK-3682 monotherapy in HCV-infected patients using a semi-mechanism based viral dynamics model.

Methods: 24 genotype (GT) 1 and 20 GT 2/3 HCV-infected treatment naïve patients were randomized to receive 4 treatments: placebo or MK-3682 at 50, 150 or 300 mg once daily (QD) for 7 days. Plasma HCV RNA levels were quantified at various time points during 35 days post treatment. A population-based KPD-viral dynamics model was developed to characterize the HCV RNA profiles. MK-3682 dose was administered in the central compartment, which was related to the amount in the effect compartment through first-order kinetics. Viral kinetics were described by a standard viral dynamics model. MK-3682 levels in the effect compartment inhibited virion production.

Results: The KPD viral dynamics model adequately described the viral kinetics profiles in the HCV-infected patients, with the viral dynamics system parameter estimates in good agreement with reported values in the literature. The individual value of the rate constant in the Dose (PK) compartment was comparable to the observed terminal elimination rate of MK-3682 prodrug in plasma. Additionally, a delay introduced by the KPD model was necessary to capture the onset of viral load decline.

Conclusions: The KPD viral dynamics model provides an adequate description of viral response after short-term monotherapy with MK-3682 in treatment-naïve HCV-infected patients. The KPD model allows for projection of MK-3682 efficacy under various conditions, and potentially can help inform the future probability of success of different formulations in development.

References: