Sequential Population PK-Viral Dynamic Modeling of TD-6450, a Next Generation Once Daily NS5A Inhibitor, following 3-Day Monotherapy in Patients with GT-1 HCV Infection

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Objectives: To investigate the PK-viral dynamic (VD) relationship for a next generation NS5A inhibitor in patients with GT-1 HCV infection following 3-day dosing with TD-6450.

Methods: A sequential PK-VD modeling approach was considered. The population PK (POP-PK) dataset consisted of two clinical studies: a SAD (0.5 to 500 mg QD)/MAD (60 to 240 mg QD) study in healthy subjects (N=80) and a 3-day dosing (60 to 240 mg QD or 240 mg BID) study in HCV patients (N=42). The effect of covariates on the PK parameters was evaluated. The individual post-hoc PK parameters were retrieved as the empirical Bayes estimates. These estimates for HCV GT-1 subjects (N=35) were used in the PK-VD modeling. The viral load data were fitted to models described in the literature with modifications for direct acting antiviral agents and use of a sigmoidal concentration-inhibitory effect relationship.

Results: The POP-PK of TD-6450 is well described by a two compartment disposition model with transit compartments for absorption and time varying bioavailability. Covariate analysis indicated a significant positive effect of BMI on the peripheral volume of distribution. The initial bioavailability (F0) was ~40% lower and the transit time (MTT) ~1h faster in the fasted state as compared to the fed state. The population viral dynamics of HCV GT-1 patients are well described by a three compartmental model with uninfected hepatocytes, infected hepatocytes, and virus as the three compartments and with proliferation terms for the hepatocytes. TD-6450 inhibits the production of the virus in a concentration dependent manner with a sub-nanomolar population mean IC₅₀. The estimates of drug independent VD parameters were in agreement with the values reported in literature.

Conclusions: The Phase-1/1b PK and PK-VD relationships are well characterized using a POP-PK modeling approach. The models may be useful in exposure-response simulations and dose selection for future trials.