A Multiple Dose Study of Raltegravir (RAL) Formulations
Matthew L. Rizk, Rajesh Krishna, Valerie Schulz, Jolanda ten Bruggencate-Broeders, Patrick Larson, Larissa Wenning
Merck & Co., Inc., West Point, PA, United States

Background: ISENTRESS (raltegravir) is an integrase strand transfer inhibitor indicated in combination with other anti-retroviral drugs for the treatment of human immunodeficiency virus (HIV-1) infection. ISENTRESS is currently marketed as a 400 mg oral compressed tablet (OCT) formulation of raltegravir given twice daily for a total daily dose of 800 mg. This study was conducted to characterize the steady state pharmacokinetic (PK) profile of 1200 mg formulations of raltegravir to support once daily administration.

Methodology: An open label, multiple dose, randomized, three period, three treatment, crossover study was performed in 24 healthy male and female subjects (18 to 55 years). Subjects received either 1200 mg once daily (QD) of the OCT formulation (3x400 mg tablets), 1200 mg QD of a reformulated raltegravir (rRAL) formulation (2x600 mg tablets), or 400 mg twice daily (BID) of the OCT for 5 days. Safety and tolerability were assessed. Full PK profiles in all cases were collected after administration under fasted conditions on days 1 and 5. In pursuing a model based drug development approach, a PK/PD viral dynamics model is being utilized to assess the feasibility of these 1200 mg formulations for once daily dosing and inform future study design.

Results: RAL was found to be generally well tolerated in healthy subjects. Administration of 1200 mg OCT QD in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 83.1 nM (53%), Cmax of 14.2 μM (99%), and AUC24hr of 49.3 μM-hr (73%). Similarly, administration of a 1200 mg rRAL tablet QD in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 81.2 nM (72%), Cmax of 20.6 μM (44%), and AUC24hr of 59.4 μM-hr (34%). Administration of 400 mg OCT BID in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 132 nM (56%), Cmax of 3.5 μM (153%), and AUC24hr (2xAUC12hr) of 26.0 μM-hr (106%).

Conclusions: Data from this study, in combination with other recently completed Phase I studies and PK/PD viral dynamics modeling and simulation, will be utilized to further assess whether QD dosing with these formulations would have a high likelihood of exerting antiviral activity similar to that of the current BID regimen, and provide insights into the feasibility of these formulations for once daily administration.