**Pharmacokinetic/pharmacodynamic (PK/PD) Characteristics of Veliparib with and without Temozolomide in Patients with Hematological Malignancies**

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**OBJECTIVES:** Veliparib is an oral inhibitor of poly (ADP-ribose) (PAR) polymerase enzyme that is currently in development for the treatment of non-hematologic and hematologic malignancies. The objectives of this analysis were a) to quantitatively describe the PK/PD characteristics of veliparib in patients with hematologic malignancies b) assess the sources of between subject variability and c) to explore the effect of temozolomide co-administration on PK/PD of veliparib.

**METHODS:** Population pharmacokinetic analysis was performed using Phoenix® NLME with rich PK data from 37 subjects after oral administration of veliparib from a Phase I study with and without temozolomide. Final PK model with covariates was validated by visual and quantitative predictive checks. Preliminary PD analysis of PAR inhibition relative from baseline was performed to assess dose-efficacy relationship.

**RESULTS:** A one-compartment model with first-order elimination and a sequential first order-zero order absorption model adequately described veliparib PK. Population mean apparent clearance (CL/F) and volume of distribution (Vd/F) were 14 L/h and 162 L, respectively. Veliparib clearance did not change after temozolomide administration. CLCR and body weight were found to be clinically significant covariates for veliparib disposition. PD analysis shows >60% inhibition of PAR levels in peripheral blood mononuclear cells (PBMCs) at doses evaluated when compared to baseline values (Figure 1) and no statistically significant dose-dependent difference was observed.

**CONCLUSIONS:** The CL/F and Vd/F estimates of veliparib were similar to those reported in literature for non-hematological malignancies [1]. Dosage adjustment of veliparib may not be required when temozolomide is co-administered. Statistically significant inhibition of PAR levels was observed after administration of veliparib at all dose levels. The developed population PK model will be utilized for exposure-efficacy (PAR inhibition) and safety (neutrophil count) analysis of veliparib.

**REFERENCE:**
Figure 1: a) Visual predictive check for Day 1 data for the final PK model. Circles represent observations, and lines represent the 5th, 50th, and 95th percentiles of observed (red) and simulated (blue) data. b) Mean PAR levels before and after veliparib (ABT) administration and with temozolomide (TMZ) addition at 20-120 mg (blue) and 150-200 mg (red) dose levels.