Population PK/PD from a Phase I Study of the Single-Agent PARP Inhibitor, Veliparib, in Patients with PARP Sensitive Tumor Types or BRCA 1/2 –Mutated Cancer

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Objective: Poly ADP ribose polymerase (PARP) is activated during DNA damage response and repair. In-vitro studies have shown that inhibitors of PARP are cytotoxic in cell-lines deficient for BRCA1/2. The PARP inhibitor, veliparib, was studied as a single-agent in known BRCA1/2 mutated tumors. The objectives of these analyses were to characterize veliparib population PK/PD by assessing typical parameter values, random and residual variabilities, covariate effects and determine if PARP is inhibited through PAR measurements.

Methods: The study enrolled 73 cancer patients who received twice daily doses of veliparib for 28 day cycles between 50- 500 mg. PK was assessed during Cycle 1 and PBMCs were collected to measure PARP activity through Cycle 4. The PK/PD analysis used nonlinear mixed-effects modeling utilizing Pharsight Phoenix® NLME and employing FOCE for final runs. Model adequacy and complexity were guided by goodness-of-fit criteria including visual inspections of diagnostic plots, successful minimumization routine convergence, parameter estimates plausibility, correlations between model estimation errors and AIC minimum objective values.

Results: Veliparib pharmacokinetics were best described using a proportional error one-compartment model. Multiple first-order error models were assessed; however, initial absorption and maximum concentrations were not adequately characterized. Numerous individual patient profiles appeared to display zero order kinetics despite oral dosing. A mixed order (first-order – zero order) absorption model with Tlag adequately described veliparib absorption. Weight and creatinine clearance covariates were incorporated into the model to explain variability. PAR measurements were integrated by applying a limited proportional error inhibition PD model as shown in the following equation:

\[ E(t) = \frac{1 - E_{max} \times C}{C + EC_{50}} \times E \]

- \( E(t) \) is the veliparib effect on the PD response at time \( t \)
- \( E_{max} \) is the maximum veliparib effect
- \( C \) is the predicted veliparib concentration
- \( EC_{50} \) is the veliparib concentration that produces half of the maximum effect

Conclusion: The PK/PD relationships show exposure-response correlations after veliparib administration. PAR expression diminished after multiple doses of veliparib, suggesting an alteration in PARP mechanism regulating cellular tumor repair. This model has been used to provide insight into the PK/PD relationships and could be utilized in simulating estimates for purposes of dose optimization or predicting response.