Population Pharmacokinetic (PopPK) and Exposure Response (E-R) Analyses for Olaparib Tablet Formulation in a Phase III study (SOLO2) in Patients with Ovarian Cancer

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Objectives: To develop a population PK model for olaparib in SOLO2 study, to evaluate and model E-R relationships for relevant efficacy and safety endpoints including progression free survival (PFS), hemoglobin concentration (Hb), and fatigue events.

Methods: Olaparib plasma concentrations, efficacy or safety endpoints including PFS, Hb and fatigue events from 94 subjects after 300 mg twice daily multiple oral tablet dosing were for analyses. A base model using a previous analysis [1] as a priori was developed for covariate modelling. The final PopPK model was used to simulate olaparib exposure for average cumulative area under concentration curve (\(\text{acAUC}\)) for E-R analyses. Hb time courses following placebo and olaparib maintenance treatment were modelled as a sigmoid \(E_{\text{max}}\) model, and an indirect response model with \(\text{acAUC}\) impacting Hb production rate constant, respectively. Fatigue events were modelled with a categorical logistic regression model. NONMEM7.3 and R3.20 were utilized for analyses.

Results: The final PopPK model adequately described observed olaparib concentrations in SOLO2 study. None of covariates evaluated including demographics, hepatic and renal function, were identified to be significant. PopPK model predicted approximately 30% lower mean AUC in SOLO2 study compared to previous analysis [1], but with individual exposure being largely overlapped. The E-R model for Hb predicted a mean change from baseline Hb of 11.6 g/dL to 10.3 g/dL at mean steady-state AUC after 6 months of treatment. The predicted probability of observing fatigue on a day without prior fatigue was 0.258% at 97.5% AUC confidence interval.

Conclusions: No covariate was identified to require \textit{a priori} dose adjustment. No E-R relationships were found for efficacy or safety endpoints, except for Hb and fatigue, for which a mild decrease in Hb or negligible increase in fatigue severity, were predicted.