Ribociclib (KISQALI®) Population Pharmacokinetics (PopPK) and Exposure-Response (E-R) Analysis of Neutropenia

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Objectives: Ribociclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that has been approved in the U.S. for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer. The recommended dose for ribociclib is 600 mg/day (3 weeks on/1 week off) irrespective of meals. Neutropenia is a reversible, dose-dependent adverse event of CDK4/6 inhibitors, including ribociclib. The analyses characterized PopPK of ribociclib and the E-R relationship between exposure and neutropenia.

Methods: PK and absolute neutrophil count (ANC) data from three clinical trials (NCT01898845, NCT01237236, NCT01872260) constituted model development datasets, and those from a phase 3 study (NCT01958021) comprised model qualification datasets. The trials enrolled patients with various advanced tumors, including breast cancer. The development of PopPK and E-R models followed the stepwise procedure from base model to full covariate model to final model. The final model was evaluated using the qualification datasets. The PopPK and E-R models were used to simulate PK and ANC profiles with ribociclib.

Results: Ribociclib PopPK was adequately described using a two-compartment model with delayed zero-order oral absorption and linear clearance with dose and body weight (BW) retained as covariates. PopPK model showed no impact of mild hepatic impairment, mild/moderate renal impairment, or proton pump inhibitors (PPIs) usage on ribociclib PK. ANC data were well described using a physiological model (Friberg et al. 2002) coupled with a log-linear drug effect model with cancer type and use of letrozole retained as covariates on the potency parameter. Both PopPK and ANC models adequately predicted the qualification datasets.

Conclusions: No dose adjustment is warranted for BW, mild hepatic impairment, or mild/moderate renal impairment. Ribociclib may be administered irrespective of PPIs. Neutropenia risk may be adequately managed and mitigated with dose reduction as suggested by model simulations.