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Objectives: To simulate the effect of decitabine on neutrophils for optimization of dose and regimen(s) of an Oral Fixed-Dose Combination (ASTX727 Low Dose) of Cytidine Deaminase Inhibitor E7727 with Decitabine for treatment of subjects with Low-Risk myelodisplastic syndromes.

Methods: A quantitative systems pharmacology (QSP) model was previously developed describing myeloblasts cell cycle; leukemic blasts, neutrophils and platelets in physiological compartments (bone marrow and blood); PK of decitabine after IV infusion, after dosing with SQ guadecitabine (SGI-110) (dinucleotide of decitabine linked to deoxyguanosine) and oral ASTX727; LINE-1 demethylation; effect of decitabine on leukemic cells, neutrophils and platelets. Model parameters were identified against in vitro and clinical data. The effect of decitabine on neutrophils was calibrated against clinical data on neutrophil counts during treatment of AML patients with guadecitabine. The model was validated against clinical data on blast dynamics in blood and bone marrow of AML patients during treatment with guadecitabine.

Results: The model was successfully calibrated and validated against various types of data. It successfully reproduces clinical data on neutrophil count changes during treatment with guadecitabine. Simulations with different doses and regimens of low-dose ASTX727 administration were performed and the model predicts that neutrophil levels depend on dose and frequency of ASTX727.

Conclusions: The model captures and predicts the pharmacodynamics of decitabine-based treatments. This model allows testing of various doses and regimens for optimization of treatment with low-dose regimens of ASTX727 to minimize decitabine-mediated neutropenia in patients with Low-Risk MDS who may be treated for longer periods than higher risk MDS.