Using semi-PBPK modeling to explore the impact of route of administration on the metabolic drug-drug interaction (DDI) between midazolam (MDZ) and erythromycin (ERY)

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Objectives: To investigate the impact of differences between intravenous (IV) and oral (PO) routes of administration for MDZ, a prototypical CYP3A substrate, and ERY, a CYP3A inhibitor, on the magnitude and time course of their metabolic DDI.

Methods: Semi-PBPK models for MDZ and ERY were developed separately, using PK parameters from clinical/in-vitro studies and published physiological parameters. The DDI model incorporated mechanism-based CYP3A inhibition (MBI) of hepatic and gut wall (GW) metabolism of MDZ by ERY, using available in-vitro/in-vivo information. The final DDI model was validated by available clinical DDI studies (no IV ERY DDI studies). The IV (1mg)/PO (3mg) MDZ AUC<sub>0-∞</sub> increase in presence of IV/PO ERY (1000 mg) at various post-ERY MDZ administration time intervals were simulated to explore DDI time-dependence. Simbiology toolbox was used for modeling and simulations.

Results: Model-predicted AUC<sub>0-∞</sub> and c<sub>max</sub> for (IV/PO) MDZ with and without PO ERY are within 30% of their observed values for all available DDI studies, confirming the validity of model and parameters. Prospective simulations demonstrate that, after IV MDZ, IV ERY consistently results in more inhibition than PO ERY (as enteric-coated (EC) tablet), due to its relatively low oral bioavailability (~40%). However, after PO MDZ, EC ERY increases MDZ AUC<sub>0-∞</sub> more than IV ERY - if MDZ is dosed later than 1 hour after ERY -, due to GW metabolic inhibition. Regardless of ERY route, PO MDZ is more sensitive to metabolic inhibition than IV MDZ, due to presystemic hepatic and GW inhibition. Despite the short ERY t<sub>1/2</sub> and as result of MBI, maximal DDI occurs when hepatic or GW CYP3A level achieves their nadir (~2-5 hours), and the DDI lasts about 4 days for IV/PO ERY.

Conclusions: Due to dual hepatic and GW inhibition of MDZ metabolism by ERY, the magnitude and time course of the DDI depends on the administration route for both drugs.