Prediction of CYP3A drug-drug interactions for DSTA4637S, an anti-
*Staphylococcus aureus* THIOMABTM antibody-antibiotic conjugate
using physiologically-based pharmacokinetic model

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**Objectives:** DSTA4637S, an anti-\textit{Staphylococcus aureus}\ THIOMABTM antibody-antibiotic conjugate, is being developed as a potential therapeutic for patients with serious \textit{Staphylococcus aureus} infections. It contains an engineered human immunoglobulin G1 anti-\textit{Staphylococcus aureus} monoclonal antibody and a rifamycin class antibiotic dmDNA31, linked through a protease cleavable linker [1]. dmDNA31 is slowly released by lysosomal protease(s) intracellularly to elicit its antibiotic property. The objective of this study was to develop a physiologically-based pharmacokinetic (PBPK) model to evaluate the potential hepatic Cytochrome P450 3A (CYP3A) drug-drug interactions (DDI) risk associated with dmDNA31 as a perpetrator, upon releasing from DSTA4637S, to support the clinical development of DSTA4637S.

**Methods:** A PBPK model linking the antibody conjugated dmDNA31 to its catabolite unconjugated dmDNA31 was developed in Simcyp (version 15) using preclinical \textit{in vitro} and \textit{in vivo} data, and then verified using clinical pharmacokinetic data from healthy volunteers intravenously administered with 5 to 150 mg/kg DSTA4637S in a Phase 1 study. The verified model was used to predict DDI between DSTA4637S and orally administered midazolam, a sensitive CYP3A4 probe substrate. Different dosing scenarios were simulated and sensitivity analysis on uncertain parameters was conducted to assess clinical DDI risk.

**Results:** The pharmacokinetic profiles of antibody conjugated dmDNA31 and unconjugated dmDNA31 following administration of DSTA4637S in healthy volunteers were well described by the developed PBPK model. The DDI simulations using this model indicated that the pharmacokinetics of midazolam would not be affected by the co-administration of DSTA4637S at the clinically relevant doses, with predicted \( C_{\text{max}} \) and AUC ratios at 1 under various scenarios simulated.

**Conclusions:** A PBPK model for antibody conjugated dmDNA31 was developed using a mixed ‘bottom-up’ and ‘top-down’ approach. The model predicted a low DDI potential of DSTA4637S interaction as a perpetrator with a sensitive CYP3A probe substrate at the clinically relevant doses.