Application of a PBPK Model to Predict Drug-Drug Interactions of Enzalutamide Due to CYP3A Induction
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Purpose
To develop and validate a mechanistic PBPK model of Enzalutamide (ENZ) and evaluate the DDI potential due to CYP3A induction by ENZ upon co-dosing with CYP3A substrates.

Methods
A minimal PBPK model of ENZ was built using the Simcyp Population-based Simulator (v13r1). Model building was accomplished using public information on ENZ, primarily from the FDA summaries. Information on its physicochemical properties, Caco-2 data, inhibition of cytochrome P450 (CYP) enzymes and transporters and human oral clearance were used for model development. The CYP induction potential of ENZ could not be completely obtained from the in-vitro hepatocyte results due to solubility limitations at clinically relevant concentrations in the hepatocyte studies. But in castrate-resistant prostate cancer patients, with ENZ dosed to steady state, the fold decline in Midazolam’s (MDZ) exposure was comparable to that routinely noted with Rifampin (600 mg, qd). Hence, Rifampin’s induction properties in Simcyp and sensitivity analysis was used to derive CYP3A induction parameters for ENZ and incorporated into the PBPK model.

Results
The simulated concentration time profiles of ENZ in healthy male subjects were comparable to observed profiles in male patients. Model predicted ENZ pharmacokinetic (PK) parameters, i.e. AUC, Cmax and half-life were within 1.5-fold of observed results obtained from two published studies (Trial 9785-CL-007 and Trial S-3100-1-01) supporting verification of the PBPK model. Model application was demonstrated by simulating a DDI trial between ENZ and MDZ, a sensitive CYP3A substrate. Upon dosing ENZ to steady state, the MDZ AUC ratio (AUC+ inducer/AUC- inducer) was 0.20 and was comparable to the observed ratio of 0.14 (Trial 9785-CL-0007). Based on model prediction, upon cessation of ENZ dosing, at least 8 weeks are needed to re-attain baseline CYP3A activity due to the long half-life of ENZ (~ 5.8 days).

Conclusion
A minimal PBPK model of ENZ was successfully developed that recapitulated it’s observed pharmacokinetics and CYP3A induction potential. Based on the PBPK model, if CYP3A substrates are co-administered with ENZ, dose adjustments of the CYP3A substrate may be required to maintain their exposure.