TITLE: DEVELOPMENT OF A PBPK MODEL FOR TBAJ-876 WITHIN THE SIMCYP POPULATION-BASED SIMULATOR AND SUBSEQUENT EVALUATION OF DDI LIABILITY AS A VICTIM OF CYP3A4 INHIBITION AND INDUCTION AND AS A PERPETRATOR OF P-GP INHIBITION.

AUTHORS: Ludwig Vincent, David Hermann, Dean Hickman, Jerry Nedelman, Hannah M Jones

Background: TBAJ-876 is being investigated for the treatment of patients with tuberculosis. TBAJ-876 is a diarylquinoline tuberculosis drug candidate developed by TB Alliance with the goal of developing a safer diarylquinoline (DARQ).

In vitro, CYP3A4 is the main enzyme responsible for CYP-mediated hepatic metabolism of TBAJ-876, and following incubation with MDCK-MDR1c cells, TBAJ-876 exhibited inhibition of P-gp.

Methods: The physiologically based pharmacokinetic (PBPK) modelling approach was therefore used to simulate plasma concentration-time profiles of TBAJ-876 following single dose and repeat dosing in healthy subjects, to evaluate the likely impact of administration of strong (itraconazole), moderate (fluconazole and erythromycin or verapamil) and weak (cimetidine) cytochrome P450 3A4 (CYP3A4) inhibitors and strong (rifampicin) and moderate (efavirenz) CYP3A4 inducers on the PK of TBAJ-876. And to evaluate the potential for transport P-gp-mediated drug-drug interactions (DDI) with TBAJ-876 as a perpetrator, effects on the sensitive probe substrates digoxin and dabigatran were simulated.

A combination of *in vitro* data and clinical PK data of TBAJ-876 in healthy subjects was used to develop the PBPK model within the Simcyp Population-Based Simulator. A minimal PBPK model with single adjusting compartment was used to model the distribution. Accounting for inbuilt inter-system extrapolation factors within Simcyp and the abundance of each individual CYP in the human liver, the fraction metabolized, fm_{CYP3A4}, was calculated to be 0.86. Observed apparent oral clearance (CL/F) data obtained from healthy subjects following a single oral dose of 100 mg with food were used in the model with *in vitro* recombinant phenotyping data to assign the relative contribution of CYP3A4 to the clearance of TBAJ-876. The *in vitro* P-glycoprotein (P-gp) transporter $K_{i,u}$ value was incorporated into the PBPK model.

Simulated PK profiles and parameters of TBAJ-876 following single and repeat oral doses (25 mg to 200 mg) to healthy subjects were in reasonable agreement with observed data (all within 1.50fold, majority within 1.25fold). The model was therefore used prospectively to predict the likely outcome of DDI.

Results: Moderate DDIs were predicted when TBAJ-876 co-administration with strong inhibitors (itraconazole) of CYP3A4 was simulated. Weak-to-moderate DDIs were predicted when TBAJ-876 co-administration with moderate CYP3A4 inhibitors (fluconazole and erythromycin) were simulated. Simulations with the strong (rifampicin) and moderate (efavirenz) CYP3A4 inducers predicted a moderate interaction.

Increases of digoxin AUCt and dabigatran AUCinf of 2% and 30%, respectively, were predicted following administration of multiple doses of TBAJ-876. *In vitro* IC_{50} values often have to be optimised to recover observed DDIs involving inhibition of P-gp-mediated efflux of digoxin. A sensitivity analysis was performed to evaluate the impact of $K_{i,u}$ on the estimated DDI magnitude. DDI simulations were repeated after reducing the $K_{i,u}$ values by 15-fold. In this case, estimated effects on digoxin and dabigran were 3% and 64%, respectively.

Conclusions: The findings from this PBPK investigation are now being used to guide the use of concomitant medications, especially antiretrovirals, in future clinical studies of TBAJ-876.