Evaluation of the drug-drug interaction between Zidovudine and Probencid by using a mechanistic kidney model (Mech KiM) nested within a full physiologically based pharmacokinetic (PBPK) model

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Background
Zidovudine (AZT) undergoes glucuronidation by UGT2B7 (65-75% of a dose) and 15-20% is eliminated unchanged in the urine. As active tubular secretion contributes significantly to the renal elimination, drug interactions of transport-mediated uptake in the kidney should be considered in parallel to metabolic drug-drug interactions (DDIs).

Objectives
The aim was to build a mechanistic PBPK model describing the metabolic and renal components of zidovudine elimination and to investigate the effect of probenecid on UGT2B7-mediated metabolism of zidovudine and Organic Anion Transporter 1 (OAT1) uptake in the kidney.

Methods
Zidovudine and Probencid PBPK models
In vitro information on the permeability, metabolism and transporter kinetics for OAT1 of zidovudine were combined with physicochemical data in a full PBPK model (Simcyp Population-based Simulator Version 14), which included a permeability-limited model for the kidney (Meh KiM) (Figure 1). In addition to hepatic and renal metabolism, renal secretion and reabsorption described by optimised transporter kinetics were also accounted for.

Simulations were run to generate plasma concentration profiles of zidovudine following single doses in healthy volunteers, asymptomatic HIV positive subjects and AIDS patients.

A full PBPK model was also developed for the UGT2B7 and OAT1 inhibitor probenecid. The ADAM (Advanced Dissolution, Absorption and Metabolism) model was utilised to describe the absorption for this compound (Figure 1). Reported in vivo CL\textsubscript{m} and CL\textsubscript{w} were used to back-calculate a metabolic intrinsic clearance using a retrograde approach. Due to the lack of in vitro fm data this was assigned as an additional human liver microsomal CL\textsubscript{int} within the model. Simulations were run to generate plasma concentration profiles of probenecid at the inhibitor dose of 500 mg.

DDI study
In vitro, K\textsubscript{int} data relating to inhibition of OAT1 in the kidney (Jung et al. 2001, Chu et al. 2007) were incorporated into the probenecid model. As in vitro UGT2B7 K\textsubscript{int} values were not available in the literature the UGT2B7 K\textsubscript{int} was optimised using a zidovudine interaction study from Hedaya et al. 1985. The models were then used to investigate the effects of probenecid (500mg q.i.d. for 2 days) on the exposure of zidovudine (2mg/kg t.i.d. for 2 days) as described by de Miranda et al. 1989.

Results
PK profiles of zidovudine and probenecid
The simulated plasma concentration profiles of zidovudine were consistent with observed data in the 3 different groups of subjects (Figures 2A, B and C). Pharmacokinetics of zidovudine are consistent in healthy volunteers and HIV positive patients with normal liver and kidney function (Barregi et al. 1994). Predicted CL\textsubscript{m} values were consistent with those reported by Sahai et al. 1984 after a 200mg dose (Figure 3A) and simulations recovered the amount excreted unchanged in urine and associated variability after a 100mg dose (Figure 3B) (Ruhnke et al. 1993). The simulated plasma concentration profiles for probenecid were consistent with observed data from 2 independent studies at a dose of 500 mg (Figure 4).

Conclusions
- PBPK modelling in conjunction with reliable in vitro data can be used to assess the importance of interactions affecting both metabolism and transport.
- Incorporation of Mech KiM within a full PBPK model for zidovudine allows mechanistic prediction of excretion in the kidney and simultaneous assessment of metabolism and transporter interactions with probenecid.
- Inhibition of UGT2B7-mediated metabolism appears to be a more significant determinant of the DDI than inhibition of renal clearance.

References
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