

# Simultaneous inhibition of glucuronidation and renal transporter pathways; a mechanistic evaluation of the interaction between zidovudine and probenecid using physiologically based pharmacokinetic (PBPK) modelling

## 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 transporter-mediated uptake in the kidney should be considered in parallel to metabolic drug-drug interactions (DDIs).

## Objectives

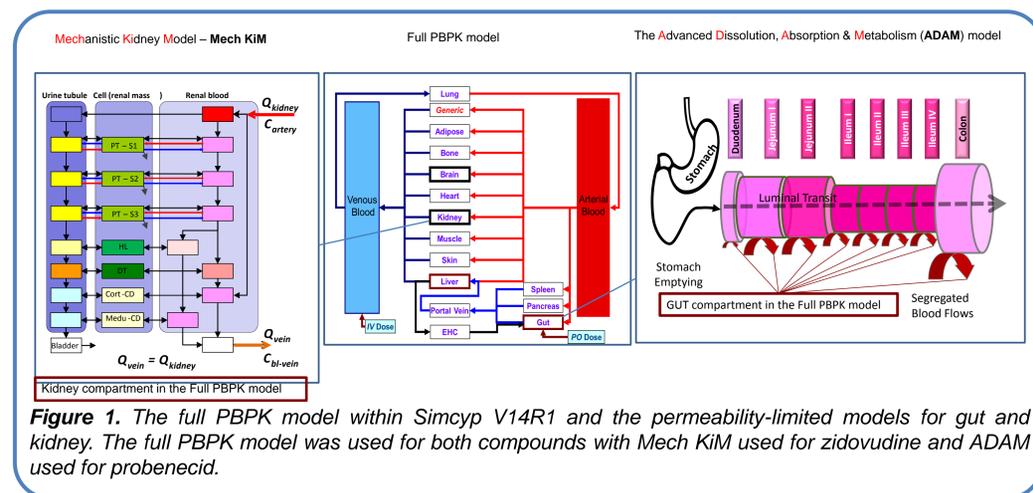
The aim was to build a mechanistic PBPK model describing the metabolic and renal disposition of zidovudine elimination to investigate the inhibitory effects of probenecid on UGT2B7-mediated metabolism of zidovudine and Organic Anion Transporter 1 (OAT1) uptake in the kidney.

## Methods

### Zidovudine and probenecid 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), with a nested permeability-limited model for the kidney (Mech KiM) (Figure 1). In addition to hepatic and renal metabolism (UGT2B7), renal filtration, saturable (OAT1) and non-saturable secretion and reabsorption were also considered.

Simulations were run to generate plasma concentrations 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*  $CL_{IV}$  and  $CL_R$  were used to back-calculate a metabolic intrinsic clearance using a retrograde approach. As *in vitro* enzymology data were not available, an additional human liver microsomal  $CL_{int}$  was assigned for the metabolism. Simulations were run to generate plasma concentration profiles of probenecid at the inhibitor dose of 500 mg.

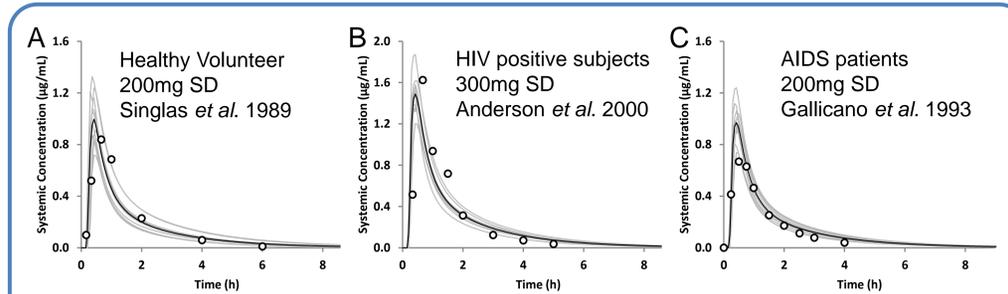
## DDI study

*In vitro*  $K_i$  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  $K_i$  values were not available in the literature, a value was derived using a zidovudine interaction study from Hedaya *et al.* 1985. Both PBPK models were applied 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) using the clinical study described by de Miranda *et al.* 1989.

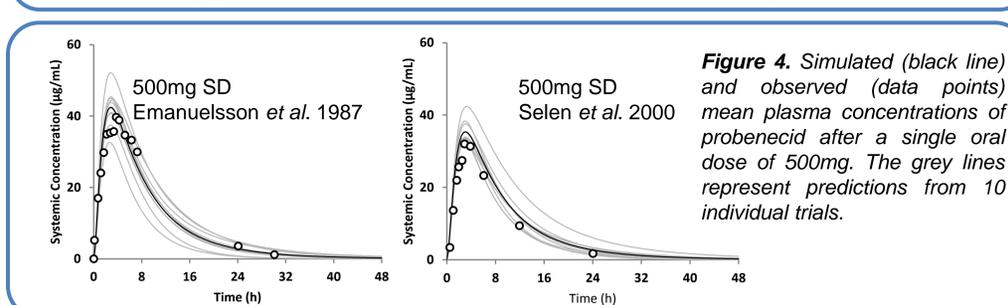
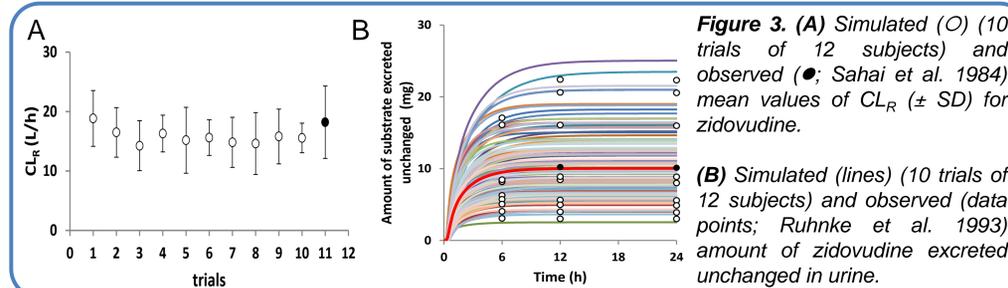
## Results

### PK profiles of zidovudine and probenecid

- The simulated plasma concentrations 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 (Bareggi *et al.* 1994).
- Predicted  $CL_R$  values of zidovudine 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 concentrations for probenecid were consistent with observed data from 2 independent studies at a dose of 500 mg (Figure 4).



**Figure 2.** Simulated (black line) and observed (data points) mean plasma concentration profiles of zidovudine after a single oral dose to (A) healthy volunteers, (B) asymptomatic HIV positive subjects and (C) AIDS patients. The grey lines represent predictions from 10 individual trials.

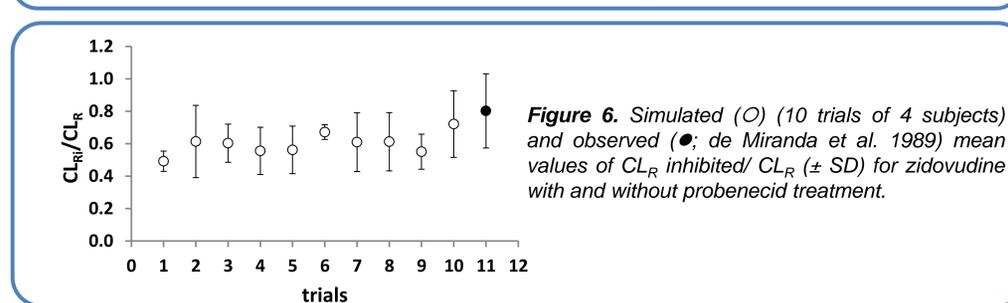
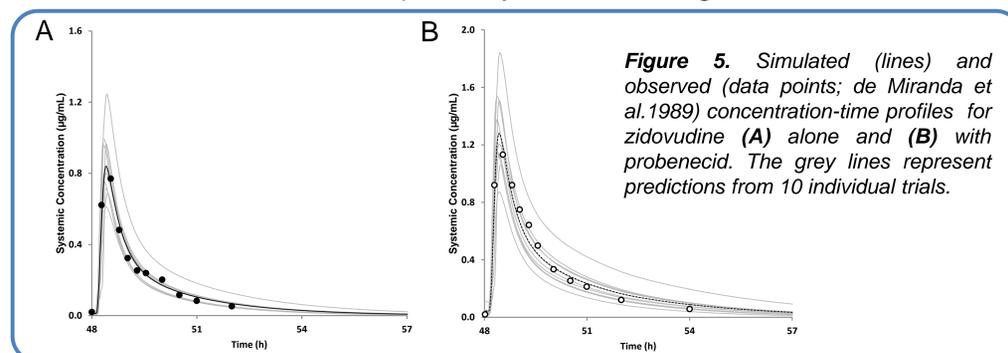


**Figure 4.** Simulated (black line) and observed (data points) mean plasma concentrations of probenecid after a single oral dose of 500mg. The grey lines represent predictions from 10 individual trials.

### UGT2B7 and OAT1-mediated DDI

The predicted increase in exposure of zidovudine following co-administration of probenecid was consistent with observed data (Figure 5).

- The mean predicted and observed AUC ratios were 1.97 (trial range 1.65 - 2.18) and 2.06, respectively.
- Ratios of  $C_{max}$  were 1.51 (trial range 1.43 - 1.56) and 1.43, respectively.
- The predicted decrease in renal clearance after probenecid treatment was similar to observed (Figure 6).
- Simulation of the DDI excluding OAT1 inhibition predicted AUC and  $C_{max}$  ratios of 1.64 and 1.39, respectively, with no change in renal clearance.



## 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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