The Impact of Genetic Polymorphism in CYP3A5 on the Pharmacokinetics of the Mixed 3A4/5 Substrates Midazolam and Tacrolimus Assessed by Clinical Trial Simulation (CTS)

H.F.Perrett¹, Z.E.Barter¹, M.S.Lennard¹, G.T.Tucker¹,² and A.Rostami-Hodjegan¹,²

Correspondence: mdp05hfp@sheffield.ac.uk

¹Academic Unit of Clinical Pharmacology, University of Sheffield, ²Simcyp Limited, Blades Enterprise Centre, Sheffield.

INTRODUCTION
- Substrates of CYP3A show large inter-individual variability in their kinetics which may be partly explained by genetic polymorphisms.
- The overlapping substrate specificities of CYP3A44 and CYP3A51,2 may confound the detection of differences in CYP3A5 genotype, particularly in studies with inadequate numbers of subjects.
- Inconsistency in the outcomes of studies reported in the literature has generated debate over the importance of CYP3A5 genotype in the metabolism of drugs such as midazolam (MDZ) and tacrolimus (TAC).

AIMS
- To assess the effect of sample size on the power of studies to detect differences in MDZ and TAC kinetics between CYP3A5 genotypes.
- To investigate the effect of the contribution of CYP3A5 to overall CYP3A metabolism on study power using a series of virtual compounds (MDZ analogues).

METHODS
- Physicochemical and in vitro metabolic data on TAC and MDZ obtained from the literature were entered into Simcyp® V7.01 (www.simcyp.com).
- The virtual analogues of MDZ differed only in the ratio of CYP3A5: CYP3A4 intrinsic metabolic clearances (ratios: 1 for MDZ and 10, 2, 0.5 and 0.1 for analogues; i.e. fM(CYP3A5), varied from 6 to 78% of total CYP3A metabolism, Figure 1).
- Substrate plasma concentration – time profiles were simulated in virtual individuals selected randomly from Caucasian populations within the Simcyp Population Library. Twenty trials of varying sizes (n = 4 - 500) were simulated.

RESULTS
- Simulated plasma drug concentration – time profiles of MDZ and TAC were consistent with those reported in clinical studies (Figure 2).
- Without enrichment, the numbers of subjects required to achieve 80% power were 80 and 24 for MDZ and TAC, respectively (Figure 3). The use of an enriched population decreased these numbers to 45 and 16, respectively.
- As expected, detection of the influence of CYP3A5 genotype in virtual MDZ analogues having a greater contribution of CYP3A5 to overall metabolism required fewer subjects.

DISCUSSION
- The simulations indicate that CYP3A5 genotype does influence the metabolism of TAC and MDZ.
- However, the number of subjects required to detect differences between CYP3A5 genotypes varies greatly depending on the ratio of CYP3A5:CYP3A4 contribution to the metabolism of the substrate.
- The lower the contribution of CYP3A5, the greater the importance of adequate study size.

CONCLUSION
- Simulations based on a knowledge of in vitro metabolism, as indicated in this study, can assist in determining appropriate study size to assess the influence of CYP3A5 polymorphism in vivo.

REFERENCES