Objectives
The aim of this study was to develop a scaling strategy for cytosolic enzymes that incorporates in vitro metabolism data with information on relative abundance in conjunction with the appropriate phenotype frequencies and demographics to simulate the range of isoniazid clearances in a virtual South African population. The use of 2 vs. 3 phenotypes to describe the population variability was also compared.

Methods
- Information relating to demographics and bodyweights in South African populations were collected from publically available databases.
- A meta-analysis was carried out for NAT-2 phenotype frequencies in South African subjects where mean values were weighted for the size of study populations.
- Clinical data were collected to provide oral and renal (\(CL_{\text{r}} = 2.76 \, \text{L/h}\)) clearance values for isoniazid [1-5].
- The in vitro intrinsic clearance for the cytosolic metabolism of isoniazid (3.13 \(\mu\text{L/min/mg}\)) was back calculated from the average oral clearance (\(CL_{\text{po}} = 26.3 \, \text{L/h}\)) in fast acetylator subjects reported by Peloquin et al.[3], using a retrograde approach.
- Relative abundances of the enzyme in fast and slow acetylators were calculated based on data reported by Weber and Hein [6] and Werely et al. [7].
- The pharmacokinetics of isoniazid were simulated in a virtual population with NAT-2 phenotype frequencies of 0.236, 0.339 and 0.425 in EM, PM and IM subjects and (B) a population of 10 trials of 14 subjects was simulated with NAT-2 phenotype frequencies of 0.236, 0.339 and 0.425 in EM, PM and IM subjects.

Results
Four studies with sufficient genetic information to classify subjects into slow, intermediate and fast phenotypes were identified (Table 1). The data from these studies were used to calculate weighted mean frequencies for each of the phenotypes. The relative activity of N-acetyltransferase in PM was set at 0.25 of the activity in extensive metabolisers [6]. When used in the activity in the IM phenotype was set to 0.61 of the activity in the EM subjects.

Two different scenarios were investigated using simulation approaches. In scenario 1 the frequency of EM, PM and IM subjects were set to 0.236, 0.339 and 0.425, respectively based on the results of the meta-analysis.

In the second scenario the frequency of EM and PM subjects was set to 0.236 and 0.764 (sum of IM & EM) respectively. The pharmacokinetics of isoniazid were simulated using a compound file constructed using the data presented in Table 2. The simulated concentrations in the two scenarios were compared to clinical data (Figure 1).

The simulations were extended to a larger virtual population (\(n = 1000\); Age 18-65; 0.5 female) and the individual oral clearance values of isoniazid were compared with those observed in the study of Werely et al. (Figure 2)

Conclusions
Using information on NAT-2 metabolism in fast acetylators, together with information on the frequency of intermediate and slow acetylator phenotypes, and relative activity of NAT-2 across phenotypes it was possible to simulate the plasma concentration-time profile and distribution of clearances of isoniazid within a South African population.

References